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(71) Applicants *(for all designated States except US)*: **GLAXOSMITHKLINE SPA** [IT/IT]; Via Alessandro Fleming, 2, I-37135 Verona (IT). **LABORATOIRE GLAXOSMITHKLINE S.A.S.** [FR/FR]; 100 route de Versailles, F-78163 Marly-le-Roi Cedex (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FARINA, Carlo** [IT/IT]; Nikem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **GAGLIARDI, Stefania** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzante di Bollate (IT). **GIARDINA, Giuseppe** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **GRUGNI, Mario** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **NADLER, Guy, Marguerite, Marie, Gerard** [FR/FR]; Laboratoire GlaxoSmithKline, 100 route de Versailles, F-78163 Marly-le-Roi Cedex (FR). **MARTINELLI, Marisa** [IT/IT]; NiKem Research srl, Via Zambeletti 25, I-20021 Baranzate di Bollate (IT).

(74) Agent: **GIDDINGS, Peter, John**; SmithKline Beecham, Corporate Intellectual Property (CN9.25.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(54) Title: QUINOLINE DERIVATIVES AS NK-3 ANTAGONISTS

(57) Abstract: Certain compounds of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof: a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

QUINOLINE DERIVATIVES AS NK-3 ANTAGONISTS

The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognises the other two receptors with lower affinity (Maggi et al, **1993**, *J. Auton. Pharmacol., 13*, 23-93).

Selective peptidic NK_3 receptor antagonists are known (Drapeau, **1990** *Regul. Pept.*, 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, *J.Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J.Neurosci.*, 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

International Patent Application, Publication number WO 00/31037 discloses certain compounds stated to be non-peptide NK-3 antagonists and also to have NK-2 antagonist activity. These compounds are disclosed to be of potential use in the prevention and treatment of a wide variety of clinical conditions, which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

We have now discovered a further novel class of potent non-peptide NK-3 antagonists some of which fall within the generic scope of WO 00/31037. The new compounds are also far more stable from a metabolic point of view than the known

peptidic NK-3 receptor antagonists and are of potential therapeutic utility. The new compounds also have good NK-2 antagonist activity and are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

These conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyper-reactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies (hereinafter referred to as the 'Primary Conditions').

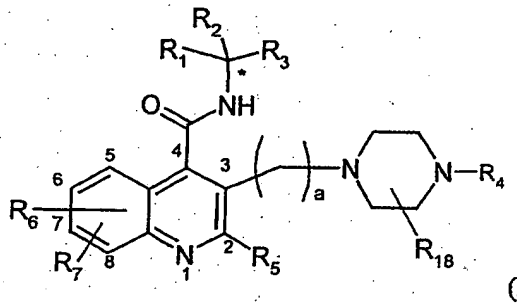
Certain of these compounds also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntingdon's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders;

reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilatation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

The new compounds also show improved oral bioavailability.

The compounds of formula (I) are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

According to the present invention, there is provided a compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

wherein:

R_1 is H or alkyl;

R_2 is aryl or cycloalkyl or heteroaryl, optionally substituted one or more times by alkyl, OH or alkoxy;

R_3 is H or alkyl or cycloalkyl or cycloalkylalkyl, optionally substituted one or more times by hydroxy or by one or more fluorines;

R_4 is H, or $-R_8R_9$ where R_8 is optionally substituted one or more times by R_{13}, or R_{19};

R_8 is alkyl or alkenyl;

R_9 is $S(O_2)R_{10}$, $S(O_2)OR_{10}$, ONO, $C(O)OR_{10}$, $C(O)NR_{11}R_{12}$, or CN;

R_{10} is H, alkyl, aryl or cycloalkyl;

R_{11} and R_{12} are independently selected from H and alkyl;

R_{13} is R_{14} or $-R_{14}R_{15}$;

R_{14} is alkyl, aryl, cycloalkyl, arylalkyl, or a five-, six-, seven- or eight-membered heterocyclic ring comprising one or more heteroatoms selected from N, O and S;

R_{15} is alkyl or $-R_{16}COOR_{17}$;

R_{16} is a single bond or alkyl;

R_{17} is H or alkyl;

R_{18} is H or up to three oxo substituents;

R_{19} is R_{20} or $-R_{20}R_{21}$;

R_{20} is alkyl, alkenyl or a single bond;

R_{21} is OH, aryl, cycloalkyl or a saturated heterocyclic ring comprising one or more heteroatoms selected from N, O and S;

R_5 is a alkyl, cycloalkyl, cycloalkylalkyl, aryl, or single or fused ring aromatic heterocyclic group, which group may be substituted one or more times by halo, hydroxy, alkyl or alkyl substituted one or more times by halo or hydroxy;

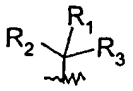
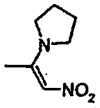
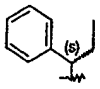
R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy or a hydroxylated derivative thereof, hydroxy, halogen, nitro, cyano, carboxy, alkylcarboxy, alkylcarboxyalkyl, haloalkyl such as trifluoromethyl, amino or mono- or di- alkylamino; or R_6 represents a bridging moiety which is arranged to bridge two adjacent ring atoms, which bridging moiety comprises alkyl or dioxyalkylene;

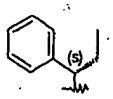
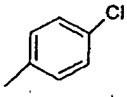
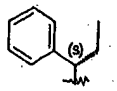
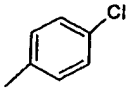
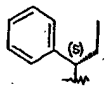
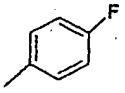
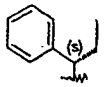
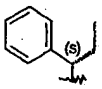
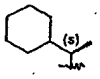
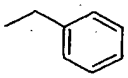
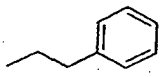
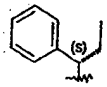
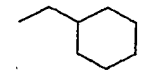
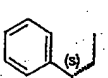
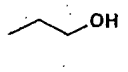
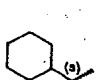
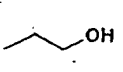
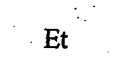
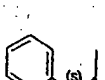
R_7 is H or halo;

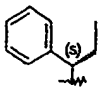
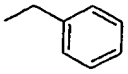
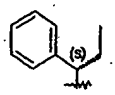
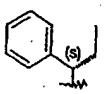
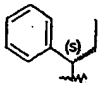
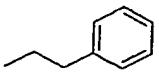
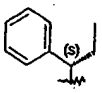
a is 1-6; and

any of R_2, R_5, R_8, R_{10}, R_{11}, R_{12}, R_{14}, R_{16}, R_{17} and R_{21} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

subject to the proviso that said compound is not a compound wherein R_7 represents H, R_5 represents unsubstituted phenyl, R_{18} is H, and R_1, R_2, R_3 and R_4 are one of the following combinations:

	a	R_4	R_6
	1		H
	1	H	H
	1	H	H
	1		H
	2		H
	3		H
	4		H

	3		H
	2		H
	2		H
	3		OMe
	1		H
	1		H
	1		H
	1		H
	1		H
	1		H
	1		H
	1	Et	H
	1	Me	H

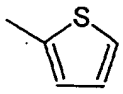
	1		H
	2	Me	H
	1	Et	H
	1		H
	3		OH

Suitably, R_3 is C_{1-6} alkyl, such a methyl, ethyl, iso-propyl, cyclopropyl, hydroxymethyl or hydroxyethyl.

Advantageously, R_2 may represent phenyl or cyclohexyl. In some preferred embodiments, R_2 represents phenyl which is substituted, suitably meta- or para-substituted, once by –OMe or –OH.

Preferably, R_1 may be hydrogen. Alternatively, R_1 may be methyl.

Suitably, R_5 may be unsubstituted phenyl. Alternatively, R_5 may be phenyl which is substituted one or more times by halo such as fluoro, or by an alkyl group which may be substituted one or more times by halo such as fluoro. Said R_5 may be phenyl which is substituted once by trihalomethyl, such as trifluoromethyl. As yet a further alternative, R_5 may be a heterocyclic ring, such as an unsaturated heterocyclic ring such as a five-membered unsaturated heterocyclic ring which comprises at least one S or N heteroatom. Said R_5 may for example be



Advantageously, R_7 may represent hydrogen.

Optionally, R_6 may represent hydrogen. Alternatively, R_6 may represent or one or more substituents selected from fluoro, chloro, bromo or trifluoromethyl. Preferably, each of said one or more substituents may be respectively positioned at the 5', 6', 7' or 8' position around the quinoline ring of said compound. As yet a further alternative, R_6 may represent one or more substituents selected from hydroxy, alkoxy such as methoxy or ethoxy or a hydroxylated derivative thereof, alkoxycarboxylate such as methoxycarboxylate or ethoxycarboxylate or an esterified derivative thereof such as methoxyethanoate ethoxyethanoate, or alkoxyamido such as methoxyamido or ethoxyamido. In particular, R_6 may represent one or more substituents selected from methyl, methoxy, ethyl, and ethoxy; preferably methoxy. Suitably, said one or more substituents may be located at the 6 and/or the 7 position around the quinoline ring. As yet a further alternative, said R_6 may represent a bridging substituent which is dioxyethylene, which bridging substituent is arranged to bridge the 6 and 7 positions around said quinoline ring.

Advantageously, a is 1, 2 or 3. Most preferably, a is 1.

In one preferred aspect of the invention, R_4 represents hydrogen.

In another preferred aspect of the invention, R_4 represents $-R_8R_9$.

Suitably, R_8 may be methyl or ethyl. Alternatively, R_8 may be ethenyl or propenyl.

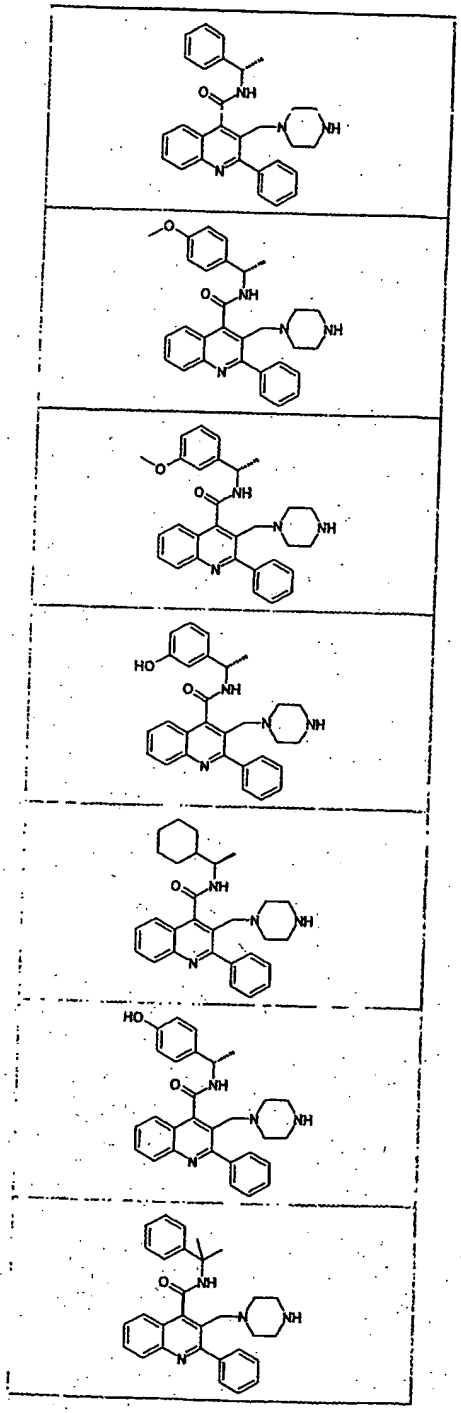
In some favourable embodiments, R_9 may be C(O)OH or $C(O)NH_2$. Alternatively, R_9 may be $S(O_2)R_{10}$, $S(O_2)OR_{10}$, or $C(O)OR_{10}$, and R_{10} may be phenyl, methyl or ethyl. As yet a further alternative, R_9 may be $C(O)NR_{11}R_{12}$ and R_{10} and R_{11} may each be the same one of methyl or ethyl.

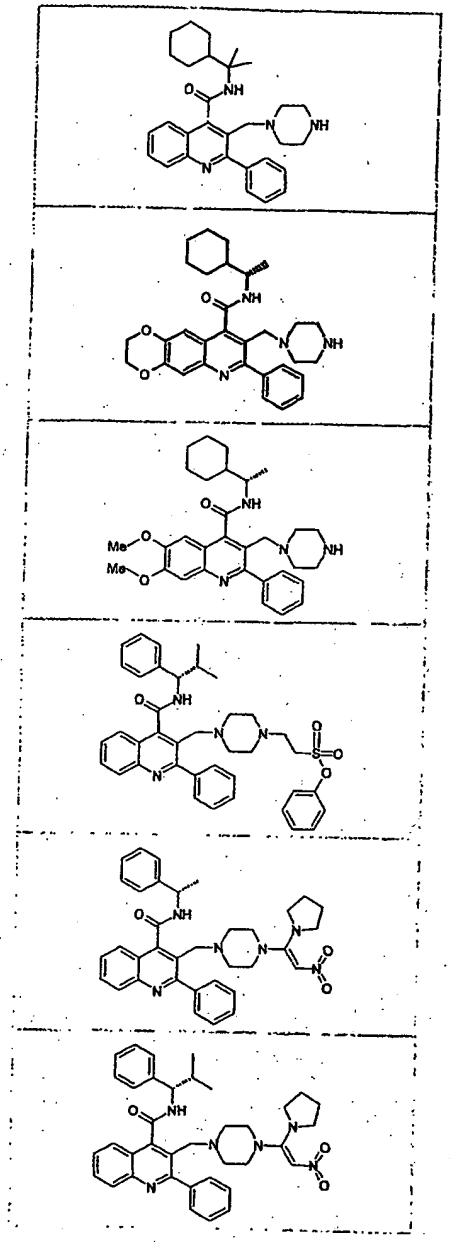
Advantageously, R_4 is branched or linear $R_8(R_{13})R_9$, where R_{13} is R_{14} or $-R_{14}R_{15}$. Suitably R_{14} is a five- or six-membered saturated heterocyclic ring. Said heterocyclic ring may comprise one or more N atoms. Optionally, said heterocyclic ring may be N-linked to said R_8. Alternatively, R_{14} may be C_{1-6} alkyl, or phenyl, or phenylmethyl, or phenylethyl. Said R_{15} may be methylethanoate, ethylethanoate, propylethanoate or butylethanoate.

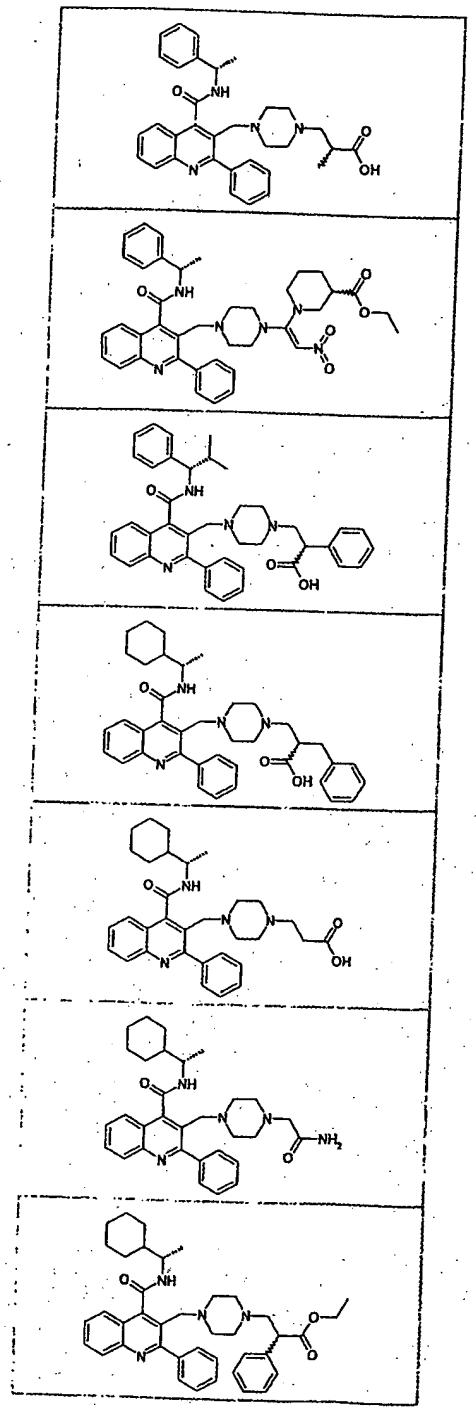
In yet another aspect of the invention, R_4 is R_{19} which is R_{20} or $-R_{20}R_{21}$. In some embodiments, R_{20} is a single bond and R_{21} is aryl such as phenyl. In other embodiments R_{20} is straight chain alkyl such as methyl, ethyl or propyl and R_{21} is OH, aryl, or a saturated heterocyclic ring comprising one or more N heteroatoms. In yet further embodiments, R_{20} is straight chain alkyl such as methyl, ethyl or propyl.

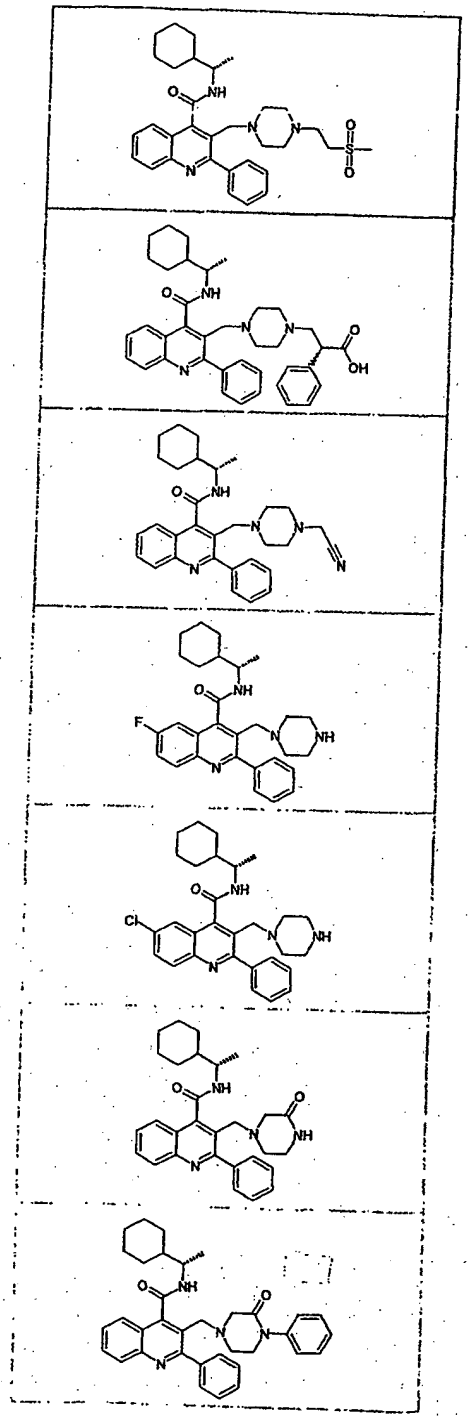
Suitably, R_{18} may be H. Alternatively, R_{18} may represent one or more oxo substituents. In many preferred embodiments, R_{18} represents one oxo substituent which is positioned at the 3', 5' or 6' position around the piperazine ring of the compound of formula (I). In other preferred embodiments, R_{18} represents two oxo substituents which are respectively positioned at the 3' and 5' or at the 3' and 6' positions around the piperazine ring of the compound of formula (I).

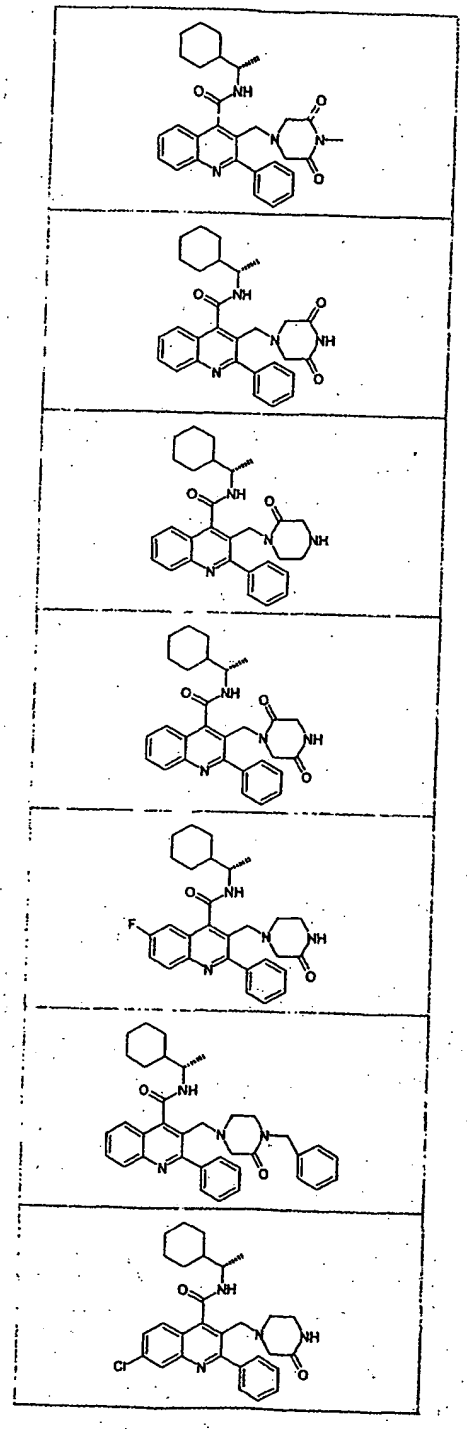
In especially preferred embodiments, the compound of the present invention is selected from the following:

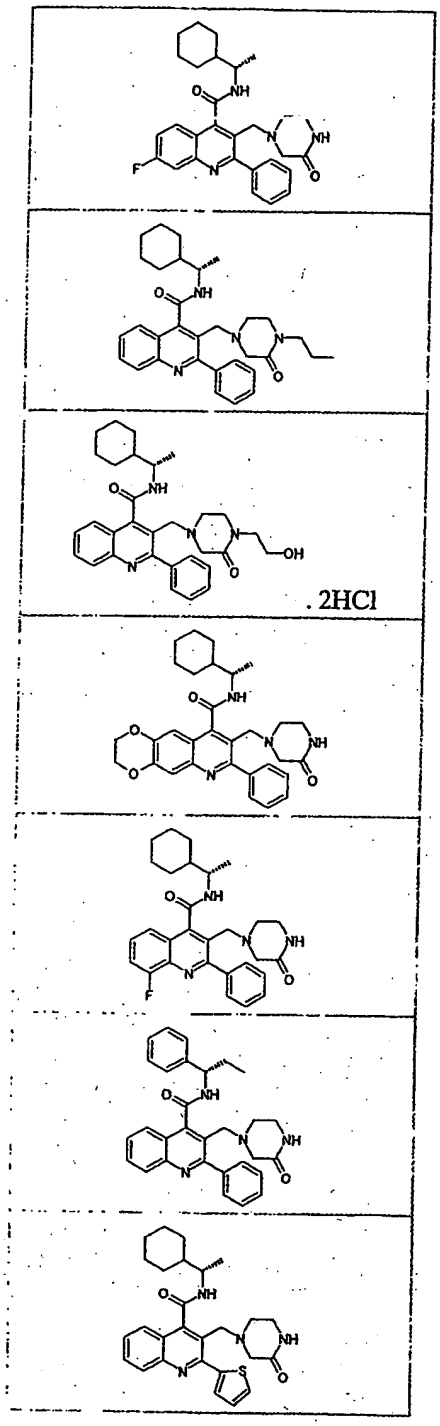


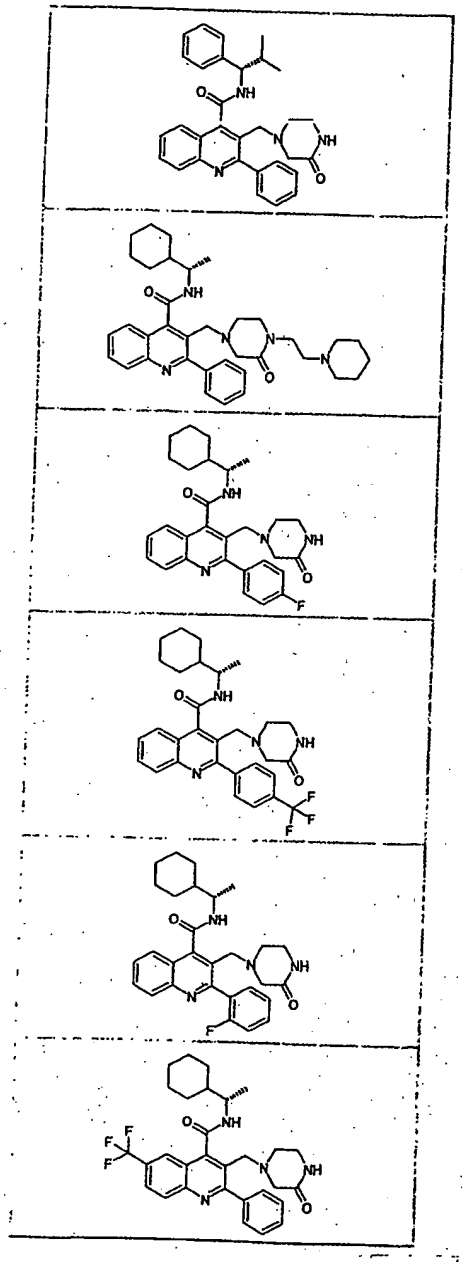


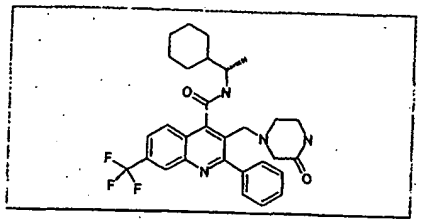




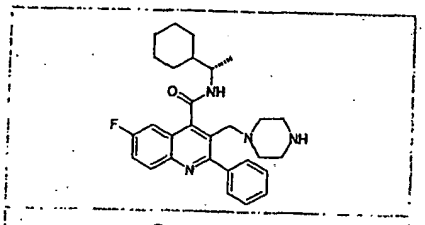


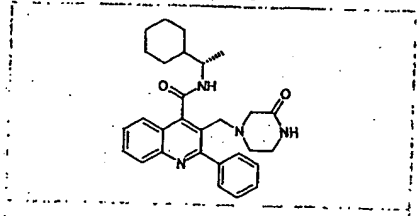

. 2HCl

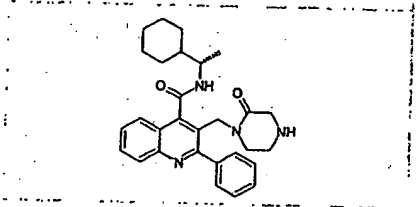


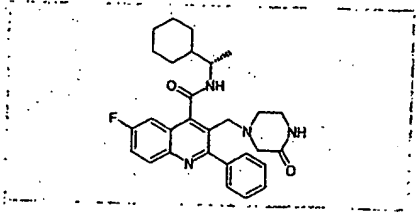


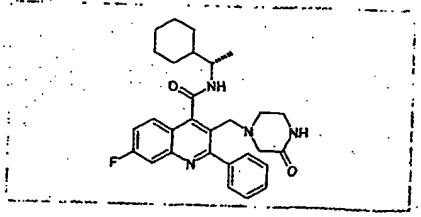
In particularly preferred embodiments, the compound of the present invention is selected from the following:

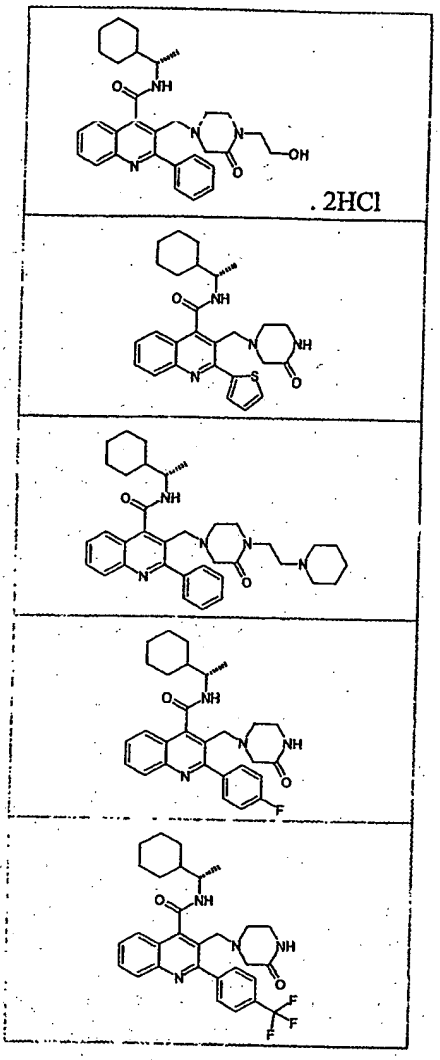




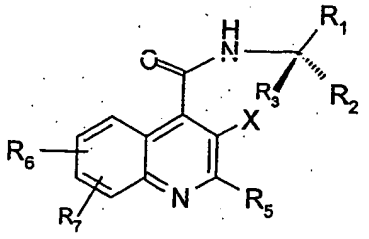






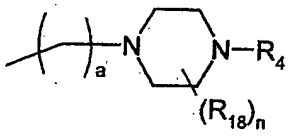


The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ia):



(Ia)

wherein R_1, R_2, R_3, R_5, R_6, and R_7 are as defined in relation to formula (I), and X represents the moiety



The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic,

phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

The term 'alkyl' (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'alkoxy' group) denotes straight- or branched-chain alkyl groups containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'carbocylic' denotes cycloalkyl and aryl rings.

The term 'cycloalkyl' denotes groups having 3 to 12, suitably 4 to 6 ring carbon atoms.

The term 'aryl' denotes aromatic groups including phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term 'aromatic heterocyclic group' denotes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N.

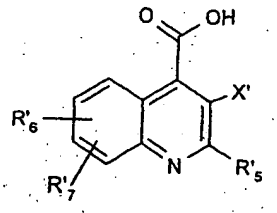
Unless specified to the contrary, suitable substituents for any heterocyclic group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

It will be understood that, unless otherwise specified, groups and substituents forming part of a compound in accordance with the invention are unsubstituted.

When used herein the term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

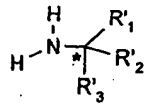
When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

The invention also provides in one aspect a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



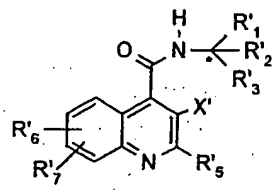
(II)

wherein R'6, R'7, R'5 and X' are R_6, R_7, R_5 and X respectively as hereinbefore defined in relation to formula (I) or (Ia), or a group convertible to R_6, R_7, R_5 and X respectively; with a compound of formula (III):



(III)

wherein R'1, R'2, and R'3 are R_1, R_2, and R_3 as defined for formula (I) or a group or atom convertible to R_1, R_2, and R_3 respectively; to form a compound of formula (Ib):



(Ib)

wherein R'1, R'2, R'3, X', R'5, R'6 and R'7 are as defined above, and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'1, R'2, R'3, X', R'5, R'6 and R'7 to R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably R'1, R'2, R'3, X', R'5, R'6 and R'7 each represents R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or a protected form thereof.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy group of the compound of formula (II) has been replaced by a different group or atom, for example by an acyl halide, preferably a chloride, or an acylazide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ib) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is prepared.

For example, the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

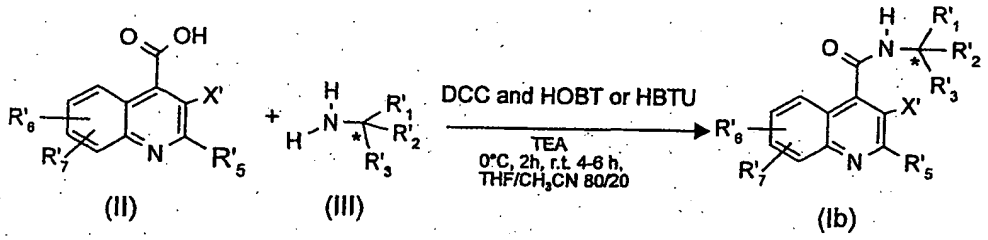
(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis*, 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a

volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 1 shown below:

Scheme 1



wherein R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are as defined above.

In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compound (II) is utilised, an hydrolysis to compound (II) is required before conversion to compound (Ib) in Scheme 1. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

It will be appreciated that a compound of formula (Ib) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ib) are useful intermediates in forming other compounds of the present invention.

Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ib) wherein at least one of R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 is not R_1, R_2, R_3, X, R_5, R_6 or R_7 respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into another compound of formula (I); and

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

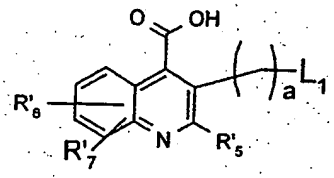
Suitably, in the compound of formula (Ib) the variables R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or they are protected forms thereof.

The above mentioned conversions, protections and deprotections are carried out using the appropriate conventional reagents and conditions and are further discussed below.

A chiral compound of formula (III) wherein R_2 is a C_5 or C_7 cycloalkyl group, R_3 is methyl and R_1 is H are described in J. Org. Chem. (1996), 61 (12), 4130-4135. A chiral compound of formula (III) wherein R_2 is phenyl, R_3 is isopropyl and R_1 is H is a known compound described in for example Tetrahedron Lett. (1994), 35(22), 3745-6.

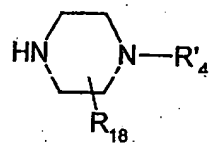
The compounds of formula (III) are known commercially available compounds or they can be prepared from known compounds by known methods, or methods analogous to those used to prepare known compounds, for example the methods described in Liebigs Ann. der Chemie, (1936), 523, 199.

In some embodiments of the invention, a compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester is prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



(IV)

wherein R'_6, R'_7, R'_5 and a are as defined above and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V):



(V)

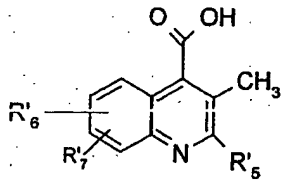
wherein R'_4 is R_4 as defined in relation to formula (I) or a protected form thereof.

Suitably, R'_4 is R_4.

Suitably, reaction between the compounds of formulae (IV) or the corresponding alkyl (such as methyl or ethyl) ester and (V) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

The compounds of formula (V) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

In cases where a is 1, a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester may be prepared by appropriate halogenation of a compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester:



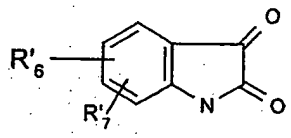
(VI)

wherein R'_6, R'_7 and R'_5 are as defined above in relation to formula (II).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

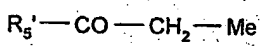
The halogenation of the compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester is suitably carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

A compound of formula (VI) is conveniently prepared by reacting a compound of formula (VII):



(VII)

wherein R'_6 and R'_7 are as defined in relation to formula (II), with a compound of formula (XIII):



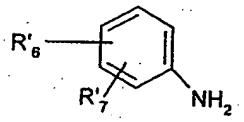
(XIII)

wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formula (VII) and (XIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

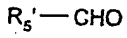
The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

Alternatively a compound of formula (VI) may be conveniently prepared by reacting a compound of formula (XIV)



(XIV)

wherein R'_6 and R'_7 are as defined in relation to formula (II), with a compound of formula (XV):



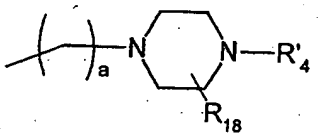
(XV)

wherein R'_5 is as defined in relation to formula (II) in presence of oxobutyric acid.

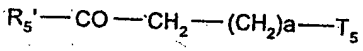
The reaction between the compounds of formula (XIV) and (XV) is conveniently carried out using Doebner reaction conditions (see for example Chem. Ber. 29, 352 (1894); Chem. Revs. 35, 153, (1944); J. Chem. Soc. B, 1969, 805), for example in an alcoholic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent.

The compounds of formula (XIV) and (XV) are known compounds or they are prepared according to methods used to prepare known compounds for example as described in *Vogel's Textbook of Practical Organic Chemistry.*

In some alternative embodiments of the invention, a compound of formula (II) wherein X' represents

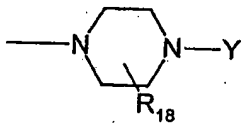


is prepared by reacting a compound of formula (VII) as defined above with a compound of formula (VIII):

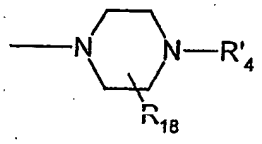


(VIII)

wherein R'_5 is as defined in relation to formula (II), and T_5 is a group

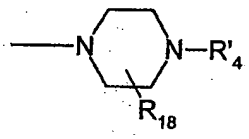


where Y is a protecting group such as a benzyl group, particularly a protecting group which is stable in basic conditions such as a terbutoxycarbonyl group, or a group R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, and a is as defined in relation to formula (II); and thereafter as required removing any protecting group, for example by dehydrogenation, and/or converting any group T_5 to



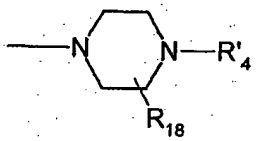
The reaction between the compounds of formula (VII) and (VIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

Protected forms of

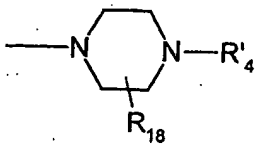


will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to

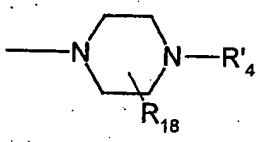


include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the

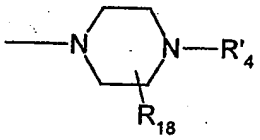


under consideration.

Suitable deprotection methods for deprotecting protected forms of

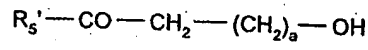


and conversion methods for converting T_5 to



will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (VIII) is prepared from a compound of formula (IX):

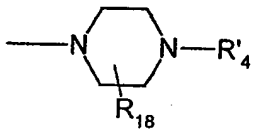


(IX)

wherein R'_5 is as defined in relation to formula (II) and a is as defined in relation to formula (VIII), by first halogenating, preferably brominating, or mesylating the compound of formula (IX) and thereafter reacting the halogenation or mesylation

product so formed with a compound capable of forming a group T_5 so as to provide the required compound of formula (VII).

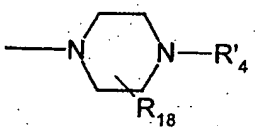
When T_5 is a group



a compound capable of forming a group T_5 is a compound of the above defined formula (V).

The halogenation of the compound of formula (IX) is suitably carried out using a conventional halogenation reagent. Mesylation is conveniently carried out using mesyl chloride in an inert solvent such as methylene dichloride, at a temperature below room temperature, such as 0°C, preferably in the presence of triethylamine.

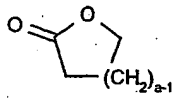
The reaction conditions between the compound of formula (IX) and the compound capable of forming a group T_5 will be those conventional conditions dictated by the specific nature of the reactants, for example when the T_5 required is a group



and the required compound capable of forming a group T_5 is a compound of the above defined formula (V), then the reaction between the halogenation or mesylation product of the compound of formula (IX) and the compound of formula (V) is carried out under analogous conditions to those described for the reaction between the compounds of formulae (IV) and (V).

Other compounds capable of forming a group T_5 will depend upon the particular nature of T_5, but will be those appropriate compounds dictated by conventional chemical practice with reference to standard texts such as Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; and Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (IX) may be prepared by reacting a compound of formula (X):



(X)

wherein a is as defined in relation to formula (VIII), with a lithium salt of formula (XI):

$$R'_5\ Li \qquad (XI)$$

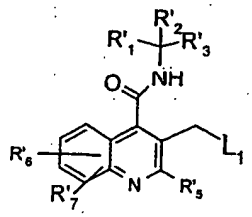
wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formulae (X) and (XI) can be carried out in an aprotic solvent, such as diethyl-ether at any temperature providing a suitable rate of formation of the required product, usually at a low temperature such as in the range of -10°C to -30°C, for example -20°C.

The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

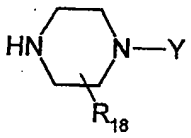
The compounds of formula (X) and (XI) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed by Krow G. R. in Organic Reactions, Vol 43, page 251, John Wiley & Sons Inc.1994 (for the compounds of formula (X)) and Organometallics in Synthesis, Schlosser M.(Ed), John Wiley & Sons Inc.1994 (for the compounds of formula (XI)).

In another aspect, the present invention provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, wherein a is 1, which process comprises reacting a compound of formula (XVI):



(XVI)

wherein each of R'_1, R'_2, R'_3, R'_5, R'_6, and R'_7 is respectively R_1, R_2, R_3, R_5, R_6, or R_7 as defined above or a group convertible to R_1, R_2, R_3, R_5, R_6, or R_7 respectively as defined above providing R'_2 is not aromatic in character, and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (XVII):



(XVII)

wherein Y is a protecting group such as a benzyl group, particularly a protecting group which is stable in basic conditions such as a terbutoxycarbonyl group, or a group R'_4, where R'_4 is R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto; and thereafter as required removing any protecting group Y, for example by dehydrogenation, and replacing the protective group Y with a group R'_4; and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 to R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Protected forms of R_4 will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to R_4 include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the R_4 under consideration.

Suitable deprotection methods for deprotecting protected forms of R_4 and conversion methods for converting R'_4 to R_4 will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitable groups convertible into other groups include protected forms of said groups.

Advantageously, a compound of formula (XVII) will be a compound of formula (V) as defined above.

Suitably R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 each represents R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively or a protected form thereof.

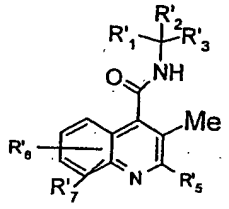
Suitable deprotection methods for deprotecting protected forms of R_1, R_2, R_3, R_4, R_5, R_6 and R_7 and conversion methods for converting R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 to R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitably, reaction between the compounds of formulae (XVI) and (XVII) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as

tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

The compounds of formula (XVII) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

A compound of formula (XVI) is prepared by appropriate halogenation of a compound of formula (XVIII):



(XVIII)

wherein R'1, R'2, R'3, R'5, R'6, and R'7 are as defined above in relation to formula (XVI).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

The halogenation of the compound of formula (XVIII) is carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C,

for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

Suitably, the compound of formula (XVIII) may be prepared by reacting a compound of formula (VI) as defined above or an active derivative thereof with a compound of formula (III) as defined above wherein R'_2 is not aromatic in character.

It is favoured if the compound of formula (VI) is present in the reaction mix as an active derivative, as hereinbefore described.

The reaction between the compound of formula (VI) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (VI) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (XVIII).

For example, the reaction between an active derivative of the compound of formula (VI) and the compound of formula (III) may be carried out:

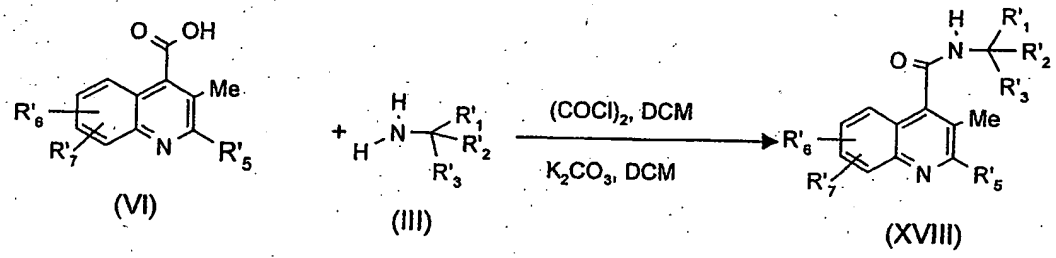
(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (VI) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable

rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 2 shown below:

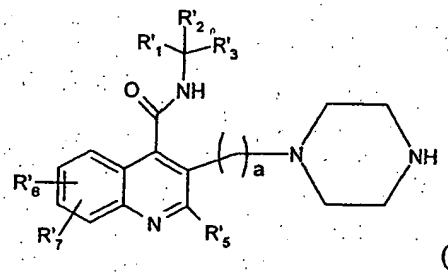
Scheme 2



(VI) (III) (XVIII)

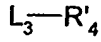
In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compounds (VI) is utilised, a hydrolysis is required before conversion to compound (XVIII) in Scheme 2. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

In yet further embodiments, compounds of formula (Ib) can be prepared by reacting a compound of formula XIX



(XIX)

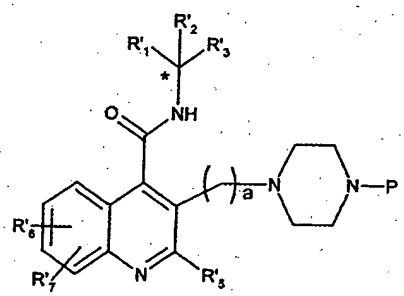
wherein R'1, R'2, R'3, R'5, R'6, R'7 and a are as defined above, with a compound of formula (XX)



(XX)

wherein L_3 represents a leaving group for example halogen or activated ester, preferably chlorine, bromine or p-nitrophenylester and R'_4 represents R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto.

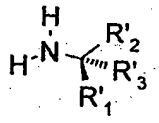
Compounds of formula (XIX) are prepared by removing the protective group of a compound of formula (XXII)



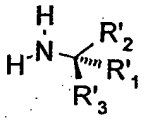
(XXII)

wherein R'_1, R'_2, R'_3, R'_5, R'_6, R'_7, and a are as defined above and P is an amine protective group, for example fmoc or benzyl, preferably fmoc. The protective group is removed by standard methods described in the literature, for example the fmoc residue is splitted by action of piperidine at room temperature in a solvent like acetonitrile.

As hereinbefore mentioned, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) can be obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

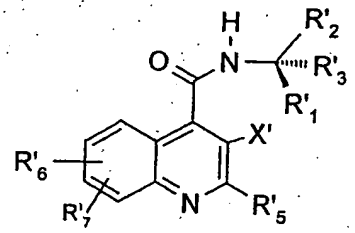


(IIIa)

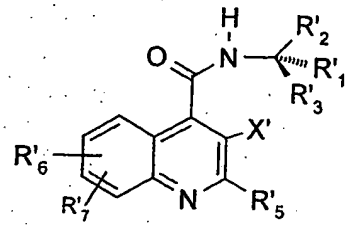


(IIIc)

wherein R'_1, R'_2 and R'_3 are as defined above, to obtain a compound of formula (I'a) or (I'c):



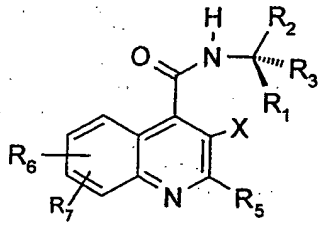
(I'a)



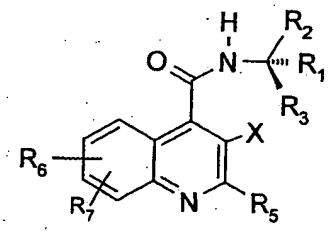
(I'c)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 are as defined above.

Compounds of formula (I'a) or (I'c) may subsequently be converted to compounds of formula (Ia) or (Ic) by the methods of conversion mentioned before:



(Ia)



(Ic)

wherein R_1, R_2, R_3, X, R_5, R_6, and R_7 are as defined above.

Suitably, in the above mentioned compounds of formulae (Ia), (Ic), (I'a), (I'c), (IIIa) and (IIIc) R_1 represents hydrogen.

An alternative method for separating optical isomers is to use conventional, fractional separation methods in particular fractional crystallization methods. Thus, a pure enantiomer of a compound of formula (I) is obtained by fractional crystallisation of a diastereomeric salt formed by reaction of the racemic compound of formula (I) with an optically active strong acid resolving agent, such as camphosulphonic acid, tartaric acid, O,O'-di-p-toluoyltartaric acid or mandelic acid, in an appropriate alcoholic solvent,

such as ethanol or methanol, or in a ketonic solvent, such as acetone. The salt formation process should be conducted at a temperature between 20°C and 80°C, preferably at 50°C.

A suitable conversion of one compound of formula (I) into a further compound of formula (I) involves converting one group X into another group X by for example:

(i) converting a ketal into a ketone, by such as mild acidic hydrolysis, using for example dilute hydrochloric acid;

(ii) reducing a ketone to a hydroxy group by use of a borohydride reducing agent;

(iii) converting a carboxylic ester group into a carboxyl group using basic hydrolysis; and/or

(iv) reducing a carboxylic ester group to a hydroxymethyl group, by use of a borohydride reducing agent.

As indicated above, where necessary, the conversion of any group R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 into R_1, R_2, R_3, X, R_5, R_6, and R_7 which as stated above are usually protected forms of R_1, R_2, R_3, X, R_5, R_6, or R_7 may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected and deprotected according to conventional chemical practice, for example as described by Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. Thus, for example suitable hydroxy protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may

be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

As indicated above, the compounds of formula (I) have useful pharmaceutical properties.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

In particular, the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

As mentioned above the Primary conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria,

coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies.

As mentioned above, the Secondary conditions include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntingdon's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilatation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter

alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatine containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions

may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatine, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which

adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, [^{125}I]-[Me-Phe^7]-NKB or [^{3}H]-Senktide, to guinea-pig and human NK_3 receptors (Renzetti et al, **1991**, *Neuropeptide, 18*, 104-114; Buell et al, **1992**, *FEBS, 299(1)*, 90-95; Chung et al, **1994**, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).

The binding assays utilised allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe^7]-NKB and [^{3}H]-Senktide specific binding to NK_3 receptor in equilibrium conditions (IC_{50}).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds

of the present invention show IC_{50} values in the range 0.1-1000 nM. The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, **1990**, *Br. J. Pharmacol., 101*, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., **1991**, *Eur. J. Pharmacol., 199*, 9-14) and human NK_3 receptors-mediated Ca^{++} mobilisation (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K_B value of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilisation induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

The activity of the compounds of the present invention, as NK-2 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK-2 ligands, [^{125}I]-NKA or [^{3}H]-NKA, to human NK-2 receptors (Aharony et al, **1992**, *Neuropeptide, 23*, 121-130).

The binding assays utilised allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-NKA and [^{3}H]-NKA specific binding to NK2 receptor in equilibrium conditions (IC_{50}).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 0.5-1000 nM, such as 1-1000 nM. The NK-2-antagonist activity of the compounds of the present invention is determined by their ability to inhibit human NK-2 receptor-mediated Ca^{++} mobilisation (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Human receptor functional assay allows the determination of the concentration of the individual compound

required to reduce by 50% (IC_{50} values) the Ca^{++} mobilisation induced by the agonist NKA. In this assay, the compounds of the present invention behave as antagonists.

The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tools. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to Tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-3 and NK-2 receptor involvement in the mediation of agonist effects in that tissue.

The following Descriptions illustrate the preparation of the intermediates, whereas the following Examples illustrate the preparation of the compounds of the invention.

Descriptions and Examples

Description 1: **3-Methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**
4-Carboxy-3-methyl-2-phenylquinoline (48.5 g , 0.184 moles) (CAS [43071-45-0]) was suspended in DCM (500 ml) and oxalyl chloride (32.1 ml, 0.368 moles) was added dropwise at R.T. under magnetic stirring. After 15 min 2 drops of DMF were added. The reaction was vigorous with gas evolution. The mixture was stirred until the solid was completely dissolved (about 30 min.). The solution was evaporated and the oxalyl chloride excess was removed dissolving in DCM and evaporating the residue several time. The crude material was redissolved in DCM (250 ml) and quickly dropped into a solution of MeOH (500 ml) in DCM (250 ml). The dark and clear solution was let stand overnight and then evaporated to dryness obtaining a light coloured solid. Ethyl

acetate and $NaHCO_3$ saturated solution was added and the mixture was stirred until the solid was completely dissolved. The layers were separated, the organic layer was washed twice with $NaHCO_3$, once with brine and then dried over Na_2SO_4, filtered and evaporated. The residue was cristallized from diethyl ether yielding 34 g of dark crystals that were in the next step used whithout further purification.

$C_{18}H_{15}NO_2$

MW = 277.32

Description 2: **3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**

3-Methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (7.2 g, 26 mmoles), prepared as in Description 1, and NBS (9.2 g, 52 mmoles) were dissolved in CH_3CN (200 ml) and warmed to incipient reflux. Dibenzoyl peroxide (about 1g) was carefully added portionwise and the solution was then refluxed for 4 h. The solution was evaporated to dryness, dissolved in ethyl acetate, washed with water, dried with Na_2SO_4, filtered and evaporated. The dark oil residue was purified by flash chromatography (eluent Hexane/Ethyl acetate= 8/2) yelding after evaporation 7.3 g of dark oil wich solidified on standing.

$C_{18}H_{14}BrNO_2$

MW = 356.23

Description 3: **Piperazine-1-carboxylic acid tert-butyl ester**

To a solution of piperazine (30 g, 350 mmol) in water (370 ml) and tBuOH (420 ml), a solution of 4N NaOH (70 ml) was added. The mixture was cooled to 0°C and then BOC_2O (38 g, 170 mmol) was added portionwise. After stirring at room temperature for 45 minutes, tBuOH was evaporated under vacuum, the precipitate (diBOCpiperazine) was filtered and water was extracted with CH_2Cl_2. After drying over Na_2SO_4 the solvent was removed under vacuum to afford the title compound as a white solid (17g, 91 mmol). Yield: 54%

$C_9H_{18}N_2O_2$

MW = 186.25

Description 4: **3-(4-tert-Butoxycarbonyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester.**

A solution of 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (8.2 g, 23 mmol), prepared as in Description 2, piperazine-1-carboxylic acid tert-butyl ester (4.7 g, 25 mmol), prepared as in Description 3, and DIEA (diisopropylethylamine, 8.5 ml, 49 mmol) in THF (200 ml) was stirred at room temperature for 66 hours. The solvent was evaporated in vacuum, the residue was then re-dissolved in ethyl acetate, washed with a saturated solution of aqueous citric acid and the organic phase dried over Na_2SO_4. After concentration of the solvent the residue (10 g) was directly used for the next step without further purification.

$C_{27}H_{31}N_3O_4$

MW = 461.56

Description 5: **3-(4-tert-Butoxycarbonyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid.**

A solution of 85% KOH (12.1g, 184 mmol) in of n-PrOH (200 ml) and 3-(4-tert-butoxycarbonyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester (10 g, 22 mmol), prepared as in Description 4, was heated to reflux, then 2 ml of water was added. Refluxing was continued for 16 hours. The mixture was concentrated to dryness in vacuum, water (100 ml) was added and washed with diethyl ether (3x 50 ml), the aqueous layer was acidified with a saturated solution of citric acid (pH 6) and then extracted with ethyl acetate. The organic layer was washed with H_2O and dried over Na_2SO_4, filtered and evaporated to dryness to give 9.4 g (21 mmol) of the title compound. Yield 95%.

$C_{26}H_{29}N_3O_4$

MW = 447.53

Description 6: **7-Methyl-6-phenyl-[1,3]dioxolo[4,5-g]quinoline-8-carboxylic acid**

3,4-Methylenedioxyaniline (20.16 g, 147 mmol) was dissolved in EtOH (300 ml) and both benzaldehyde (14.3 ml, 147 mmol) and 2-oxobutirric acid (15 g, 147 mmol) were added. The solution was stirred at room temperature for three days. A solid was formed

which was collected by filtration and dissolved in NaOH 1 M. The solution was washed with Et_2O and acidification of the aqueous phase a solid precipitated. The solid was filtered by suction and dried in vacuum oven to yield the title compound (25 g) as a pale brown solid.

$C_{18}H_{13}NO_4$

MW = 307.30

MP= >300°C

Description 7: **7-Methyl-6-phenyl-[1,3]dioxolo[4,5-g]quinoline-8-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

7-Methyl-6-phenyl-[1,3]dioxolo[4,5-g]quinoline-8-carboxylic acid (10 g, 32.5 mmol), prepared as in Description 6, was suspended in CH_2Cl_2 (200 ml) and cooled to 0-5°C. Oxalyl chloride (5.8 ml, 65 mmol) was added dropwise under stirring in 15 min. After adding few drops of DMF, the mixture was allowed to warm to room temperatureand left for 3 h. The organic solvent was evaporated to dryness. The crude residue was dissolved with CH_2Cl_2 and added dropwise to a stirred suspension of (S)-1-cyclohexylethylamine (5.8 ml, 39.05 mmol) and K_2CO_3 (9 g) in CH_2Cl_2 (150 ml). The solid was filtered and the organic solvent was evaporated to dryness. The crude residue was purified by flash chromatography (eluent hexane:AcOEt 6:4) obtaining 2.8 g of the title compound as a yellow solid.

$C_{26}H_{28}N_2O_3$

MW = 416.52

Description 8: **4-[9-((S)-1-Cyclohexyl-ethylcarbamoyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-8-ylmethyl]-piperazine-1-carboxylic acid tert-butylester**

7-Methyl-6-phenyl-[1,3]dioxolo[4,5-g]quinoline-8-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (1.5 g, 3.5 mmol), prepared as in Description 7, and N-bromosuccinimmide (1.26 g, 7 mmol) were suspended in CCl_4 (60 ml) and warmed to incipient reflux. Dibenzoyl peroxide (about 10 mg) was carefully added and the solution

was then refluxed for 2 h. The solvent was removed under vacuum and the residue was re-dissolved in CH_3CN (30 ml). This solution was added dropwise to a mixture of piperazine-1-carboxylic acid tert-butyl ester (1.3 g, 7 mmol), prepared as in Description 3, and K_2CO_3 (1 g, 7 mmol) in CH_3CN (45 ml). The mixture was refluxed overnight. The organic solvent was evaporated to dryness, re-dissolved in AcOEt and washed with water, 10% citric acid and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified on column chromatography to yield 1.33 g of the title compound.

$C_{36}H_{46}N_4O_5$

MW = 614.78

Description 9: **4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-6,7-dimethoxy-2-phenyl-quinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester**

This compound was prepared starting from 3,4-dimethoxyaniline and following the procedure described in Description 6-8.

Description 10: **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester**

6.6 g (18.5 mmol) of crude 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 2) were dissolved, under nitrogen atmosphere, in 100 ml of dry THF. The solution was cooled to 10 °C and 6.8 g (20 mmol) of Fmoc piperazine, dissolved in 50 ml of THF, were added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Salts were filtered off and the filtrate was evaporated *in vacuo* to dryness, taken up with 2 N HCl and washed with EtOAc; the aqueous layer was basified with 10% NaOH and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo* to dryness to obtain a crude material. Flash chromatography on silica gel afforded 7.5 g (yield: 69%) of the title compound.

$C_{37}H_{33}N_3O_4$

MW = 583.68

^{1}H NMR (DMSO-d_6) δ: 1.99 (4H); 3.10 (4H); 3.62 (2H); 3.97 (3H); 4.20 (1H); 4.42 (2H); 7.18-7.40 (4H ar); 7.45-7.92 (12H ar); 8.09 (1H ar)

Description 11: **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid hydrochloride**

7.5 g (13 mmol) of the ester of Description 10 were dissolved in 150 ml of 6 N HCl and refluxed for 1 h. Evaporation to dryness afforded 9.5 g of crude title compound, which was used in the following reaction without further purification.

$C_{36}H_{31}N_3O_4.HCl$

MW = 606.12

^{1}H NMR (DMSO-d_6) δ: 2.50 (4H); 3.32 (4H); 4.22 (2H); 4.23 (1H); 4.35 (2H); 6.50 (1H exch with D_2O); 7.22-7.88 (14H ar); 7.98 (1H ar); 8.17 (2H ar)

Description 12 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

A mixture of 5 g (7.8 mmol) N-fmoc-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid (compound of Description 11), 3.14 g (31 mmol) triethylamine, 4.44 g (11.7 mmol) HBTU, 100 ml anhydrous THF, 1.18 g (11.7 mmol) (S)-(+)-1-cyclohexylethylamine and 65 ml methylene chloride was stirred one night at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and the organic phase washed with water. After drying over $MgSO_4$ the solvent was concentrated and the residue purified by flash chromatography over 350 g silicagel (eluent: first heptane/ethyl acetate: 2/1 then 1/1) to afford 4 g (yield 74%) of the title compound.

$C_{44}H_{46}N_4O_3$

MW = 678.87

^{1}H-NMR ($CDCl_3$) δ: 0.70-1.95 (m, 14H); 1.98-2.25 (m, 4H); 2.95-3.42 (m, 4H); 3.75 (s, 2H); 4.17 (t, 1H); 4.28 (m, 1H); 4.38 (d, 2H); 6.95-7.80 (m, 16H); 8.05 (d, 1H ar); 8.15 (d, 1H ar)

Description 13: **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

6.95 g (10.8 mmol) of crude acid of Description 11 were condensed with 2 g (13.5 mmol) of (S)-2-methyl-1-phenyl propylamine following the procedure of Description 12 affording, after flash chromatography on silica gel, 5.4 g (yield 71%) of the title compound.

$C_{46}H_{44}N_4O_3$

MW = 700.86

^1H NMR ($CDCl_3$) δ: 0.96 (3H); 1.18 (3H); 1.56-2.98 (4H); 2.28 (1H); 3.04 (4H); 3.53 (2H); 4.20 (1H); 4.35 (2H); 5.17 (1H); 7.18-7.63 (18H ar); 7.74 (3H ar); 7.97 (1H exch with D_2O); 8.14 (1H ar)

Description 14: **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide**

Synthesised starting from the compound of Description 11 and following the procedure of Description 12.

$C_{44}H_{40}N_4O_3$

MW = 672.83

Description 15: **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

A mixture of 4 g (5.8 mmol) of N-fmoc-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 12), 160 ml acetonitrile and 890 microliters (9 mmol) piperidine was stirred one night at room temperature. The solvent was concentrated and the residue purified by flash chromatography on 150 g silicagel (eluent: first CH_2Cl_2/MeOH: 9/1 then CH_2Cl_2/MeOH/NH_4OH: 9/1/0.1) to afford 1.86 g (70.2%) of the title compound.

$C_{29}H_{36}N_4O$

MW = 456.63

^{1}H-NMR ($CDCl_3$) δ: 0.85-1.55 (m, 9H); 1.56-1.98 (m, 5H); 2.00-2.25 (m, 4H); 2.50-2.85 (m, 4H); 3.73 (s, 2H); 4.24 (m, 1H); 7.28-7.78 (7H ar); 7.80-8.19 (4H)

Description 16 : **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

5.4 g (7.7 mmol) of the Fmoc derivative of Description 14 were reacted with 1.25 ml of piperidine in 200 ml acetonitrile, at room temperature for one night. The reaction mixture was concentrated to dryness and the residue was purified by flash chromatography on silicagel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$; 90/10/2), affording 2.55 g (yield 69.3%) of the title compound.

$C_{31}H_{34}N_4O$

MW = 478.64

^{1}H NMR (DMSO-d_6) δ: 0.79 (3H); 1.06 (3H); 1.49-2.55 (9H); 3.45 (2H and 1H exch with D_2O); 4.88 (1H); 7.12-8.10 (14H ar); 9.16 (1H exch with D_2O)

Description 17: **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide**

Synthesised starting from the compound of Description 14 and following the procedure of Description 15.

$C_{29}H_{30}N_4O$

MW = 450.58

Description 18: **3-[4-(1-Methylsulfanyl-2-nitro-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide**

A solution of 0.39 g (0.865 mmol) of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide (compound of Description 17) and 0.14 g (0.865 mmol) of 1,1-bis-methylsulfanyl-2-nitro-ethene in a mixture of 7.5 ml of ethanol and 1.8 ml of DMF was heated to reflux for 15 h. The solvents were concentrated and the residue was purified by flash chromatography on silicagel (eluent: heptane/AcOEt : 1/1) to afford 0.13 g of the title compound as yellow crystals.

$C_{32}H_{33}N_5O_3S$

MW = 567.71

^{1}H-NMR ($CDCl_3$) δ: 1.72 (d, 3H); 1.85-2.21 (m, 4H); 2.34 (s, 3H); 2.87-3.22 (m, 4H); 3.66 (s, 2H); 5.55 (m, 1H); 6.52 (s, 1H); 7.19-7.67 (m, 12H); 7.78 (td, 1H ar); 8.00 (d,1H ar); 8.14 (dd, 1H ar)

Description 19 : **3-[4-(1-Methylsulfanyl-2-nitro-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

Starting from 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide (compound of Description 16) and following the procedure of Description 18 afforded the title compound.

$C_{34}H_{37}N_5O_3S$

MW = 580.73

^{1}H-NMR ($CDCl_3$) δ: 0.94 (d, 3H); 1.22 (d, 3H); 1.74-2.18 (m, 4H); 2.20 (m, 1H); 2.35 (s, 3H); 2.98-3.27 (m, 4H); 3.52 (s, 2H); 5.13 (m, 1H); 6.53 (s, 1H); 6.85 (d, 1H ar); 7.15-7.65 (m, 11H); 7.74 (t,1H ar); 7.92 (br, 1H); 8.14 (d, 1H)

Description 20: **2-Benzyl-3-{4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid ethyl ester (racemic)**

A solution of 0.40 g (0.87 mmol) 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 15) and 0.33 g (1.75 mmol) of 2-phenyl-but-3-enoic acid ethyl ester in 10 ml isopropanol was heated to reflux for 48 h. A white suspension appeared but TLC monitoring proved the reaction to be not completed. Additional 100 mg of 2-phenyl-but-3-enoic acid ethyl ester were the added and the reflux continued for 4 h. The solvent was concentrated and the residue was purified by flash chromatography over silicagel (eluent: CH_2Cl_2/MeOH:95/5) affording 0.17 g of the title compound.

$C_{41}H_{50}N_4O_3$

MW = 646.87

^{1}H-NMR ($CDCl_3$) δ:1.07 (t, 3H); 1.16 (m, 5H); 1.27 (d, 3H); 1.40 (m, 1H); 1.65-1.95 (m, 5H); 2.00-2.45 (8H); 2.50-2.96 (m, 5H); 3.72 (2H); 3.99 (q, 2H); 4.27 (m, 1H); 7.02-7.30 (m, 5H ar); 7.46 (m, 5H ar); 7.58 (td, 1H ar); 7.73 (td, 1H ar); 8.05-8.18 (m, 2H ar); 8.22 (broad band, 1H)

Description 21 :**3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid ethyl ester**

Following the procedure of Description 20 but starting from 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide (compound of Description 16) and using 2-phenyl-acrylic acid ethyl ester afforded the title compound. (reaction yield : 47%, conversion yield : 70%).

$C_{42}H_{46}N_4O_3$

MW = 654.85

^{1}H-NMR ($CDCl_3$) δ: 0.94 (d, 3H); 1.07-1.22 (6H); 1.65-2.48 (m, 10H); 3.04 (t, 1H); 3.55 (s, 2H); 3.67 (m, 1H); 4.07 (m, 2H); 5.16 (m, 1H); 7.14-7.61 (m, 16H ar); 7.71 (td, 1H ar); 8.02 (d, 1H ar); 8.12 (dd, 1H ar); 8.50 (br, 1H)

Description 22: **3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid tert-butyl ester**

The title compound was obtained starting from 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 15) and t-butyl acrylate, following the procedure of description 21.

$C_{36}H_{48}N_4O_3$

MW = 584.80

^{1}H-NMR ($CDCl_3$) δ: 0.95-1.95 (m, 13H); 1.28 (d, 3H); 1.40 (s, 9H); 2.02-2.68 (m, 10H); 3.75 (s, 2H); 4.25 (m, 1H); 7.44 (m, 5H ar); 7.58 (td, 1H ar); 7.74 (td, 1H ar); 8.02-8.19 (m, 2H ar); 8.28 (br, 1H)

Description 23: **6-Fluoro-3-methyl-2-phenylquinoline-4-carboxylic acid**

To a solution of 5-fluoroisatin (3 g, 0.018 moles) (CAS [443-69-6]) in EtOH (100 ml), KOH in pellets (4.7 g, 0.08 moles) was added. The mixture was stirred for 30 minutes at room temperature, then 1-phenylpropan-1-one (CAS [93-55-0]) (2.4 g, 0.018 moles) was added and the solution was refluxed for additional 4 hours.
The solvent was evaporated under vacuum and the residue was dissolved in water (200 ml), the water was extracted with ethyl ether (200 ml) and the aqueous solution was acidified with a saturated solution of citric acid. The obtained precipitate was filtered and dried in vacuum oven to yield the title compound (3 g) as a pale yellow solid. Yield 63%
$C_{17}H_{12}FNO_2$
MW = 281.29

Description 24: **6-Fluoro-3-methyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)amide**
6-Fluoro-3-methyl-2-phenylquinoline-4-carboxylic acid (2 g, 7.6 mmol), prepared as in Description 23, was suspended in CH_2Cl_2 (20 ml) and cooled to 0-5°C. Oxalyl chloride (1.5 ml, 25 mmol) was added drop-wise under stirring in 15 min. After adding few drops of DMF, the mixture was allowed to warm to room temperature and left for 3 h. The organic solvent was evaporated to dryness. The crude residue was dissolved with CH_2Cl_2 and added drop-wise to a stirred suspension of (S)-1-cyclohexylethylamine (1.5 ml, 10 mmol) and K_2CO_3 (3 g) in CH_2Cl_2 (10 ml). The solution was refluxed for 3 hours then concentrated under vacuum. The residue was re-dissolved in AcOEt and the organic layer was washed with a solution of 1 M NaOH, with a saturated solution of NaCl and finally dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was triturated with diisopropylether obtaining 2.3 g of the title compound as a pale yellow solid. Yield 76%.
$C_{25}H_{27}FN_2O$
MW 390.51

Description 25: **3-Bromomethyl-6-fluoro-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

6-Fluoro-3-methyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (1.4 g, 0.003 moles), prepared as in Description 24, and NBS (1.3 g, 0.0076 moles) were dissolved in CCl_4 (50 ml) and warmed to incipient reflux. Dibenzoyl peroxide (about 1g) was carefully added portion-wise and the solution was then refluxed for 2 h. The solution was evaporated to dryness, dissolved in ethyl acetate, washed with a 10% solution of Na_2CO_3, dried with Na_2SO_4, filtered and evaporated. The dark oil residue was purified by flash chromatography (eluent hexane/ethyl acetate = 8/2) yielding after evaporation 1.3 g of a pale yellow solid. Yield 77%.

$C_{25}H_{26}BrFN_2O$

MW = 469.40

Description 26: **4-[4-((S)-1-cyclohexylethylcarbamoyl)-6-fluoro-2-phenylquinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester**

A solution of : 3-bromomethyl-6-fluoro-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)amide (0.3 g, 0.6 mmol; compound prepared as in Description 25), piperazine-1-carboxylic acid tert-butyl ester (0.13 g, 0.7mmol) and ethyldiisopropylamine (0.3 ml, 1.8 mmol) in dry THF (30 ml) was stirred for 24 h at room temperature. The solvent was evaporated to dryness in vacuo and the residue was re-dissolved in EtOAc. This mixture was washed with a dilute NaOH solution, with water and dried over Na_2SO_4. After evaporating to dryness, the residue was purified by flash chromatography to afford 0.25 g of the desired compound. Yield 72%

$C_{34}H_{43}FN_4O_3$

MW = 574.75

Description 27: **{Carboxymethyl-[4-((S)-1-cyclohexylethylcarbamoyl)-2-phenylquinolin-3-ylmethyl]amino}-acetic acid**

A solution of 3-bromomethyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (5 g, 11 mmol, prepared from isatine (CAS [91-56-5]) according to Description 23-25), (carboxymethylamino)acetic acid (2.2 g, 16 mmol) and ethyldiisopropylamine (14 ml, 80 mmol) in acetonitrile (100 ml) was stirred at room temperature for 12 hours. The solvent was evaporated under vacuum, a solution of 2N

NaOH was added and the obtained precipitated was filtered. The organic layer was neutralized with 1N HCl and extracted with EtOAc.The organic layer was dried over Na_2SO_4, filtered and evaporated to give the title compound (4 g). Yield: 72%

$C_{29}H_{33}N_3O_5$

MW = 503.60

Description 28: **4-[4-((S)-1-Cyclohexylethylcarbamoyl)-2-phenylquinolin-3-ylmethyl]-3-oxopiperazine-1-carboxylic acid tert-butyl ester**

NaH (0.09 g, 3.4 mmol) was added portion-wise at room temperature to a suspension of 3-oxo-piperazine-1-carboxylic acid tert-butyl ester (0.6 g, 3 mmol, CAS [76003-29-7]) in DMF (10 ml) and DMSO (3 ml), . The obtained dark solution was stirred for 30 minutes then a solution of 3-bromomethyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (1.3 g, 2.8 mmol, prepared from isatine (CAS [91-56-5]) according to Description 23-25) in DMF (5 ml) was added. The mixture was stirred for additional 3 hours and then was poured in a saturated solution of NaCl. The obtained precipitate was filtered by suction and dried in vacuum oven to yield the title compound (1 g, 1.7 mmol). Yield 63%

$C_{34}H_{42}N_4O_4$

MW = 570.74

Description 29: **8-Methyl-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid**

Benzaldehyde (6.7 ml, 66 mmol) was added drop-wise to a solution of 2,3-dihydrobenzo[1,4]dioxin-6-ylamine (10 g, 66 mmol) in EtOH (200 ml). The solution was refluxed for 1 hour and then 2-oxobutyric acid (6.7 g, 66 mmol) was added portion-wise. The mixture was refluxed for additional 3 hours and then left at room temperature overnight. The obtained precipitate was filtered to give 13 g of the title compound. Yield 61%

$C_{19}H_{15}NO_4$

MW = 321.34

Description 30: **8-Bromomethyl-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid methyl ester**

The compound was prepared following the procedure of Description 1 and 2 starting from 8-methyl-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid (prepared as in Description 29).

$C_{20}H_{16}BrNO_4$

MW: 414.26

Description 31: 8-(3-Oxo-piperazin-1-ylmethyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid methyl ester

A solution of : 8-bromomethyl-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid methyl ester (414 mg, 1 mmol, prepared as in Description 30), piperazin-2-one (CAS [5625-67-2]) (0.1 g, 1 mmol) and ethyldiisopropylamine (0.3 ml, 1.8 mmol) in dry THF (30 ml) was stirred for 24 h at room temperature. The solvent was evaporated to dryness in vacuo and the residue was re-dissolved in AcOEt. This mixture was washed with a dilute NaOH solution, with water and dried over Na_2SO_4. After evaporating to dryness, the residue was purified by flash chromatography (eluent Ethyl acetate/ Methanol/ NH_3 = 90/10/0.1) to afford 0.3 g of the desired compound.

Yield 69%

$C_{24}H_{23}N_3O_5$

MW: 433.47

Description 32: 8-(3-Oxo-piperazin-1-ylmethyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid

A solution of 85% KOH (0.46 g, 7 mmol) and 8-(3-oxo-piperazin-1-ylmethyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid methyl ester (0.5 g, 1.2 mmol, prepared as in Description 31), in MeOH (20 ml), was heated to reflux for 36 hours then citric acid (1.47 g, 7 mmol) was added. The inorganic salts were filtered and the MeOH was evaporated. The crude solid was triturated with ether to give 0.4 g of the title compound.

$C_{23}H_{21}N_3O_5$

MW = 419.44

General procedure for the preparation of Examples 1-3, 5, 7, 8.

A solution of of 3-(4-tert-butoxycarbonyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid (2 g, 4.5 mmol), prepared as in Description 5, suitable amine (5.7 mmol), DCC (1.2 g , 5.8 mmol) and DMAP (0.7 g, 5.8 mmol) in of CH_2Cl_2 (60 ml) was stirred for 24 h at room temperature. The resultant solid was filtered and the filtrate was evaporated to dryness. The residue was re-dissolved in AcOEt, washed with a 10% NaCl solution and dried over $MgSO_4$. After concentration of the solvent, the crude product was dissolved in CH_2Cl_2 (60 ml) and TFA (3 ml) was added. The red solution was stirred at room temperature overnight; then the solvent and the excess of TFA were removed under vacuum. The residue was dissolved in H_2O and washed 2 times with Et_2O. The water extract was made alkaline by addition of 2N NaOH solution and the product was extracted with AcOEt. The solvent was evaporated to dryness and the residue was purified by flash chromatography (eluent CH_2Cl_2: MeOH 93:7) to afford the title compound (yield: 30-50%).

Example 4: **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(3-hydroxy-phenyl)-ethyl]-amide**

To a solution of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-amide (300 mg, 0.62 mmol), compound of Example 3, in CH_2Cl_2 (20 ml), BBr_3 (0.020 ml, 0.31 mmol) of was added at 0°C. After stirring the solution overnight at room temperature, the solvent was removed under vacuum. The residue was redissolved in AcOEt and washed with Na_2CO_3 20% solution. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (eluent: CH_2Cl_2/MeOH/NH_4OH 90:10:1) to afford the title compound.

Example 6: **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(4-hydroxy-phenyl)-ethyl]-amide**

The title compound was prepared starting from the Example 2 following the procedure of Example 4.

Example 9: **7-Phenyl-8-piperazin-1-ylmethyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

To a solution of 4-[9-((S)-1-Cyclohexyl-ethylcarbamoyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-8-ylmethyl]-piperazine-1-carboxylic acid tert-butylester (1.25 g, 2 mmol), prepared as in Description 8, in CH_2Cl_2 (50 ml), TFA (2 ml) was added dropwise at room temperature. Stirring was continued overnight. The solvent was evaporated under vacuum and the residue was basified K_2CO_3 saturated solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified on column chromatography (CH_2Cl_2/MeOH/NH_4OH 90:10:1) to give the title compound (0.45 g).

Example 10: **6,7-Dimethoxy-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The title compound was prepared following the procedure of Example 9 starting from the compound described in Description 9.

Example 11: **2-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-ethanesulfonic acid phenyl ester**

A solution of 0.092 g (0.5 mmol) of phenyl vinylsulfonate in 2 ml of methylene chloride was cooled by an ice bath. Then 0.24 mg (0.5 mmol) of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide (compound of Description 16) were added portionwise. Stirring was maintained 30 min at the temperature of the ice bath followed by 3 h at room temperature.

The solvent was concentrated and the residue was purified by flash chromatography on silicagel (eluent : AcOET/heptane : 1/1) to afford 200 mg (60.5 %) of the title compound as a white amorphous solid.

Example 12: **3-[4-(2-Nitro-1-pyrrolidin-1-yl-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide.**

Starting form 3-[4-(1-methylsulfanyl-2-nitro-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide (compound of Description 18) and 1 g of pyrrolidine in 10 ml acetonitrile was refluxed for 4 h. The solvent was concentrated, the residue dissolved in ethyl acetate, the organic phase washed with water, dried over $MgSO_4$ and concentrated again. The residue was purified by flash chromatography on silicagel (eluent: first AcOEt, then AcOEt/MeOH:9/1). The residue obtained after concentration of the desired fractions was triturated in diethyl ether affording 75 mg (73%) of the title compound as yellow crystals.

Example 13: **3-[4-(2-Nitro-1-pyrrolidin-1-yl-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

Starting from 3-[4-(1-methylsulfanyl-2-nitro-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide (compound of Description 19) and following the procedure of Example 12 afforded the title compound as orange crystals.

Example 14: **2-Methyl-3-{4-[2-phenyl-4-((S)-1-phenyl-ethylcarbamoyl)-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid.**

A solution of 0.25 g (0.54 mmol) of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide (compound of Description 17) and 0.13 g (0.8 mmol) of trimethylsilyl methacrylate (Aldrich) in 5 ml dry chloroform was heated at 65°C for 24 h. After cooling, 1 ml of methanol was added and the mixture stirred for 10 min. The solvent was concentrated and the residue was purified by flash chromatography on silicagel (eluent : first CH_2Cl_2/MeOH : 95/5; then CH_2Cl_2/MeOH : 90/10). The desired fractions were pooled, the solvent concentrated and the residue was crystallised in diethyl ether to afford the title compound as white crystals.

Example 15: **1-(2-Nitro-1-{4-[2-phenyl-4-((S)-1-phenyl-ethylcarbamoyl)-quinolin-3-ylmethyl]-piperazin-1-yl}-vinyl)-piperidine-3-carboxylic acid ethyl ester.**
Starting form 3-[4-(1-methylsulfanyl-2-nitro-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide (compound of Description 18) and following the procedure of Example 12 but replacing the pyrrolidine by ethyl nipecotate afforded the title compound as a yellow amorphous solid.

Example 16: **3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid**
A mixture of 0.26 g (0.4 mmol) of 3-{4-[4-((S)-2-methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid ethyl ester (compound of Description 21) , 0.42 ml of 1N aqueous LiOH and 2.5 ml of ethanol was stirred at room temperature for 24 h, the 0.3 ml of LiOH solution were added again and stirring was continued for 6 h. 20 ml of AcOEt were added followed and the mixture was stirred with a saturated aqueous solution of $KHSO_4$. The organic phase was decanted and washed with water. The aqueous phase was extracted twice with CH_2Cl_2, the organic phases were pooled , dried over $MgSO_4$ and concentrated. The residue was purified twice by flash chromatography on silicagel (eluent: CH_2Cl_2/MeOH : 92/8) to afford 100 mg of the title compound as white crystals.

Example 17: **2-Benzyl-3-{4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid (racemic)**
A solution of 0.16 g (0.25 mmol) of racemic 2-benzyl-3-{4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid ethyl ester (compound of Description 20) and 250 microliters of aqueous 1 N LiOH in 10 ml ethanol was stirred at room temperature for 48 h. Meanwhile 100 ml of 1 N LiOH were added twice. The solvent was concentrated and the residue taken-up in 15 ml CH_2Cl_2 and washed with an aqueous saturated solution of $KHSO_4$. After drying over $MgSO_4$ the solvent was concentrated and the residue (0.19 g) was purified by flash

chromatography over silicagel (eluent: CH_2Cl_2/MeOH:95/5) affording 0.073 g of the title compound as white solid.

Example 18: **3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid**

A mixture of 0.38 g (6.4 mmol) of 3-{4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid tert-butyl ester (compound of Description 22), 5 ml of methylene chloride and 5 ml of trifluoroacetic acid was stirred at room temperature for 4 h. The solvent was concentrated and the residue, after neutralisation with 1N aqueous NH_4OH, was purified by flash chromatography on silicagel (eluent: first CH_2Cl_2/MeOH:95/5, then 90/10) afforded the title compound as white crystals.

Example 19: **3-(4-Carbamoylmethyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

A mixture of 0.5 g (1.1 mmol) of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 15), 15 ml of anhydrous THF, 0.23 g (1.6 mmol) of bromoacetamide and 286 ul (1.6 mmol) of diisopropylethyl amine was stirred at room temperature for 16 h. The solvent was concentrated and the residue was dissolved in AcOEt. The organic phase was thoroughly washed with water, dried over $MgSO_4$ and concentrated affording the title compound as white crystals.

Example 20: **3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid ethyl ester**

Starting from 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 15) and following the procedure of description 21) afforded the title compound as a white solid. yield 85.6 %

Example 21: **3-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

A mixture of 0.3 g (0.66 mmol) of 2-phenyl-3-piperazin-1-yimethyi-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (compound of Description 15), 120 ul (1.4 mmol) of methylvinyl sulfone and 7 ml of isopropanol was stirred at reflux for 15 h. The solvent was concentrated and the residue was purified by flash chromatography over 40 g silicagel (eluent: CH_2Cl_2/MeOH:96/4) affording the title compound as white crystals.

Example 22: **3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid**

Applying the procedure of Example 17 to the ester of Example 20 afforded the title compound as white crystals.

Example 23: **3-(4-Cyanomethyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

Using the procedure of Example 19 but replacing the bromoacetamide by bromoacetonitrile afforded the title compound as a white solid.

Example 24: **6-Fluoro-2-phenyl-3-piperazin-1-ylmethylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

TFA (3 ml) was added dropwise at room temperature to a solution of 4-[4-((S)-1-cyclohexylethylcarbamoyl)-6-fluoro-2-phenylquinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester (0.25 g, 0.4 mmol, compound prepared in Description 26) in CH_2Cl_2 (20 ml). Stirring was continued for additional 3 hours. The solvent was concentrated under vacuum and the residue was basified with 1N NaOH solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated to give, after triturating with diisopropyl ether, the title compound (0.15 g).Yield: 79%

Example 25: **6-Chloro-2-phenyl-3-piperazin-1-ylmethylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl) amide**

The compound was prepared following the procedure of Example 24, according to the Description 23-26 starting from 5-chloroisatin (CAS [17630-76-1]).

Example 26: **3-(3-Oxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

A solution of : 3-bromomethyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (0.3 g, 0.7 mmol; compound prepared from isatine (CAS [91-56-5]) according to Description 23-25), piperazin-2-one (0.1 g, 1 mmol, CAS [5625-67-2]) and ethyldiisopropylamine (0.3 ml, 1.8 mmol) in dry THF (30 ml) was stirred for 24 hours at room temperature. The solvent was evaporated to dryness in vacuo and the residue was re-dissolved in AcOEt. This mixture was washed with a dilute NaOH solution, with water and dried over Na_2SO_4. After evaporating to dryness, the residue was purified by flash chromatography (eluent Ethyl acetate/ Methanol/ NH_4OH = 90/10/0.1) to afford 0.2 g of the desired compound. .Yield 60%

Example 27: **3-(3-Oxo-4-phenylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 1-phenylpiperazin-2-one and 3-bromomethyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (prepared from isatine (CAS [91-56-5]) according to Description 23-25).

Example 28: **3-(4-Methyl-3,5-dioxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

A solution of {carboxymethyl-[4-((S)-1-cyclohexylethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]amino}-acetic acid (0.1 g, 0.2 mmol, prepared as in Description 27) in acetamide (4 ml) was stirring for 8 hours at 160°C then a saturated solution of NaCl was added . The mixture was extracted with EtOAc and the organic layer was dried over

Na_2SO_4, filtered and evaporated to give, after purification by flash chromatography (eluent: hexane/ethyl acetate = 6/4), 50 mg of the title compound. Yield: 50%

Example 29: **3-(3,5-Dioxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

A solution of {carboxymethyl-[4-((S)-1-cyclohexylethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]amino}-acetic acid (0.1 g, 0.2 mmol, prepared as in Description 27) in 30% solution of NH_3 (15 ml) was evaporated to dryness. The obtained yellow solid compound was heated for 3 hours at 170°C. The crude compound was purified by flash chromatography (eluent: hexane/ethyl acetate = 6/4) to give 54 mg of the title compound. Yield: 56%.

Example 30: **3-(2-Oxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

To a solution of 4-[4-((S)-1-Cyclohexylethylcarbamoyl)-2-phenylquinolin-3-ylmethyl]-3-oxopiperazine-1-carboxylic acid tert-butyl ester (0.5 g, 1 mmol, prepared as in Description 28) in CH_2Cl_2 (20 ml), TFA (2 ml) was added drop-wise at room temperature. Stirring was continued overnight. The solvent was evaporated under vacuum and the residue was basified with a saturated solution of K_2CO_3 and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified on column chromatography (CH_2Cl_2/MeOH/NH_4OH = 90:10:1) to give the title compound (0.3 g). Yield 63%

Example 31: **3-(2,5-Dioxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)1-cyclohexylethyl)-amide**

NaH (0.06 g, 2.2 mmol) was added portion-wise at room temperature to a suspension of piperazine-2,5-dione (0.5 g, 4 mmol, CAS [106-57-0]) in DMF (10 ml) and DMSO (3 ml). The dark solution was stirred for 30 minutes then a solution of 3-bromomethyl-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (1 g, 2.2 mmol, prepared from isatine (CAS [91-56-5]) according to Description 23-25) in DMF (5 ml) was added. The mixture was stirred for additional 4 hours and then was poured in a

saturated solution of NaCl. The obtained precipitate was filtered by suction and dried in vacuum oven to yield the title compound (0.5g, 1 mmol). Yield 45%

Example 32: **6-Fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 13 starting from 3-bromomethyl-6-fluoro-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (prepared from 5-fluoroisatine (CAS [443-69-6]) according to Description 23-25).

Example 33: **3-(4-Benzyl-3-oxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

NaH (0.006 g, 2.2 mmol) was added portion-wise at 0°C to a suspension of 3-(3-oxo-4-phenylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (1 g, 2.2 mmol, prepared as in Example 26) in DMF (10 ml). The dark solution was stirred for 10 minutes at 0°C and then a benzylbromide (0.26 ml, 2.2 mmol) was added dropwise. The mixture was stirred for additional 2 hours at room temperature and then was poured in a saturated solution of NaCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified on column chromatography (Ethyl Acetate / hexane = 4/6) to give the title compound (0.7 g) as a pale yellow solid. Yield 57%

Example 34: **7-Chloro-3-(3-oxopiperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-7-chloro-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (prepared from 6-chloroisatin (CAS [6341-92-0]) according to Description 23-25).

Example 35: **7-Fluoro-3-(3-oxopiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-7-fluoro-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (prepared from 6-fluoroisatine (CAS [324-03-8]) according to Description 23-25).

Example 36: **3-(3-Oxo-4-propyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

NaH (0.006 g, 2.2 mmol) was added portion-wise at 0°C to a suspension of 3-(3-oxo-4-phenylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (1 g, 2.2 mmol, prepared as in Example 26) in DMF (10 ml). The dark solution was stirred for 10 minutes at 0°C and then propylbromide (0.27 g, 2.2 mmol) was added drop-wise. The mixture was stirred for additional 2 hours at room temperature and the was poured in a saturated solution of NaCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified on column chromatography (Ethyl Acetate / hexane = 4/6) to give the title compound (0.5 g) as a pale yellow solid. Yield 44%

Example 37: **3-[4-(2-Hydroxyethyl)-3-oxopiperazin-1-ylmethyl]-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide dihydrochloride**

NaH (0.024 g, 0.6 mmol) was added portion-wise at 0°C to a suspension of 3-(3-oxo-4-phenylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (0.24 g, 0.5 mmol, prepared as in Example 26) in DMF (2 ml). The dark solution was stirred for 10 minutes at 0°C and then a solution of 2-(2-bromo-ethoxy)tetrahydropyran (0.1 g, 0.5 mmol, CAS [17739-45-6]) in THF (2 ml) was added drop-wise. The mixture was stirred for additional 2 hours at room temperature, poured in a saturated solution of NaCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude residue was re-dissolved in MeOH (4 ml) and a solution of HCl in Et_2O (0.5 ml) was added at 0°C. The mixture was stirred for additional 15 minutes at 0°C. The solvent was evaporated to give 150 mg of the title compound. Yield:58%.

Example 38: **8-(3-Oxo-piperazin-1-ylmethyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

A solution of 8-(3-oxopiperazin-1-ylmethyl)-7-phenyl-2,3-dihydro[1,4]dioxino[2,3-g]quinolinecarboxylic acid (100 mg, 0.25 mmol, prepared as in Description 32) TEA (0.14 ml, 1 mmol) and HBTU (95 mg, 0.25 mmol) was stirred for 30 minutes at room temperature. 0.075 ml of (S)-1-cyclohexylethylamine was added at room temperature and the reaction was left to stir overnight. The solvent was evaporated under vacuum and the solid was re-dissolved in ethyl acetate and washed with water, 10% $NaHCO_3$ and a saturated solution of NaCl; the organic layer was evaporated and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH = 99/1/0.1) to give 80 mg of the title compound. Yield 60%

Example 39: **8-Fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-8-fluoro-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (prepared from 7-fluoroisatine (CAS [317-20-4]) according to Description 23-25).

Example 40: **3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-propyl)-amide**

The compound was prepared following the procedure of Example 38 starting from (S)-1-phenylpropylamine and 3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid (prepared from 3-Methyl-2-phenyl-quinoline-4-carboxylic acid (CAS [43071-45-0]) according to Description 30-32).

Example 41: **3-(3-Oxo-piperazin-1-ylmethyl)-2-thiophen-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-2-thiophen-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-

amide (prepared from 1-thiophen-2-yl-propan-1-one (CAS [13679-75-9]) and isatine CAS [91-56-5] according to Description 23-25).

Example 42: **3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

The compound was prepared following the procedure of Example 38 starting from (S)-2-methyl-1-phenylpropylamine and 3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid (prepared from 3-methyl-2-phenylquinoline-4-carboxylic acid (CAS [43071-45-0]) and according to Description 30-32).

Example 43: **3-[3-Oxo-4-(2-piperidin-1-ylethyl)piperazin-1-ylmethyl]-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)amide**

The compound was prepared following the procedure of Example 33 starting from 1-(2-chloro-ethyl)piperidine (CAS [1932-03-2]) and 3-(3-oxo-4-phenylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide (prepared as in Example 26).

Example 44: **2-(4-Fluorophenyl)-3-(3-oxopiperazin-1-ylmethyl)-quinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 1-(4-fluorophenyl)propan-1-one (CAS [456-03-1]) and isatin (CAS [91-56-5]) according to Description 23-25).

Example 45: **3-(3-Oxopiperazin-1-ylmethyl)-2-(4-trifluoromethylphenyl)quinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 1-(4-trifluoromethylphenyl)-propan-1-one (CAS [711-33-1]) and isatin (CAS [91-56-5]) according to Description 23-25).

Example 46: **2-(2-Fluorophenyl)-3-(3-oxopiperazin-1-ylmethyl)-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting 1-(2-fluorophenyl)-propan-1-one (CAS [446-22-0]) and isatin (CAS [91-56-5]) according to Description 23-25).

Example 47:**3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-6-trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-2-phenyl-6-trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (prepared from 5-trifluoroisatine (*Tetrahedron Letters*, 35, 7303, **1994**) according to Description 23-25).

Example 48: **3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-7-trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

The compound was prepared following the procedure of Example 26 starting from 3-bromomethyl-2-phenyl-7-trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (prepared from 6-trifluoroisatine (*Tetrahedron Letters*, 35, 7303, **1994**) according to Description 23-25).

TABLE 1

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
1		$C_{29}H_{30}N_4O$	198-202°C	- 31.06 (c=0.5, MeOH)
2		$C_{30}H_{32}N_4O_2$	109-111°C	- 28.56 (c=0.5, MeOH)
3		$C_{30}H_{32}N_4O_2$	147-153°C	- 43.22 (c=0.5, MeOH)

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
4		$C_{29}H_{30}N_4O_2$	240-244°C	- 33.83 (c= 0.5, MeOH)
5		$C_{29}H_{36}N_4O$	118-120°C	- 14.4 (c= 0.5, MeOH)
6		$C_{29}H_{30}N_4O_2$	163°C	--
7		$C_{30}H_{32}N_4O$	--	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
8		$C_{30}H_{38}N_4O$	--	--
9		$C_{31}H_{38}N_4O_3$	135-137°C	- 7.87 (c= 0.15, MeOH)
10		$C_{31}H_{40}N_4O_3$	130-132°C	+ 33.31 (c= 0.25, MeOH)
11		$C_{39}H_{42}N_4O_4S$	--	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
12		$C_{35}H_{38}N_6O_3$	164-165°C	--
13		$C_{37}H_{42}N_6O_3$	170-175°C	--
14		$C_{33}H_{36}N_4O_3$	137-138°C.	--
15		$C_{39}H_{44}N_6O_5$	120-121°C	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
16		$C_{40}H_{42}N_4O_3$	156-158°C	--
17		$C_{39}H_{46}N_4O_3$	136°C	--
18		$C_{32}H_{40}N_4O_3$	192-195°C.	--
19		$C_{31}H_{39}N_5O_2$	125-130°C	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
20		$C_{40}H_{40}N_4O_3S$	90-91°C	--
21		$C_{32}H_{42}N_4O_3S$	120-121°C	--
22		$C_{38}H_{44}N_4O_3$	144-145°C	--
23		$C_{31}H_{37}N_5O$	96-98°C	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[\alpha]_D^{20}$
24		$C_{29}H_{35}FN_4O$	154-158°C	+ 7.54 (c= 0.1, MeOH)
25		$C_{29}H_{35}ClN_4O$	> 250°C	- 7.24 (c= 0.5, MeOH)
26		$C_{29}H_{34}N_4O_2$	--	--
27		$C_{35}H_{38}N_4O_2$	--	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
28		$C_{30}H_{34}N_4O_3$	--	--
29		$C_{29}H_{32}N_4O_3$	124°C	+ 5.83 (c= 0.1, MeOH)
30		$C_{29}H_{34}N_4O_2$	212°C	- 5.83 (c= 0.1, MeOH)
31		$C_{29}H_{32}N_4O_3$	251°C	- 7.23 (c=0.1, MeOH)

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
32		$C_{29}H_{33}FN_4O_2$	230°C	+ 5.8 (c= 0.1, MeOH)
33		$C_{36}H_{40}N_4O_2$	181°C	+ 8.36 (c=0.5, MeOH)
34		$C_{29}H_{33}ClN_4O_2$	140-142°C	--
35		$C_{29}H_{33}FN_4O_2$	163-165°C	+ 12.34 (c= 0.5, MeOH)

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[\alpha]_D^{20}$
36		$C_{32}H_{40}N_4O_2$	150°C	+ 11.36 (c= 0.5, MeOH)
37		$C_{31}H_{38}N_4O_3$. 2 HCl	171-173°C	+ 16.06 (c= 0.1, MeOH)
38		$C_{31}H_{36}N_4O_4$	144-145°C	-
39		$C_{29}H_{33}FN_4O_2$	165°C	+ 22.67 (c= 0.1, MeOH)

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
40		$C_{30}H_{30}N_4O_2$	160°C	- 47.17 (c=0.1, MeOH)
41		$C_{27}H_{32}N_4O_2S$	225-230°C	+ 8.5 (c=0.2, MeOH)
42		$C_{31}H_{32}N_4O_2$	137°C	- 47.99 (c=0.1, MeOH)
43		$C_{36}H_{47}N_5O_2$	160°C	- 4.9 (c= 0.1, MeOH)

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
44		$C_{29}H_{33}FN_4O_2$	--	+ 10.16 (c=0.3, EtOH)
45		$C_{30}H_{33}F_3N_4O_2$	214-217°C	+ 9.1 (c=0.2, MeOH)
46		$C_{29}H_{33}FN_4O_2$	167-169°C	+ 14.4 (c= 0.5, MeOH)
47		$C_{30}H_{33}F_3N_4O_2$	--	--

Ex.	Molecular Structure	Molecular Formula	Melting Point	$[a]_D^{20}$
48		$C_{30}H_{33}F_3N_4O_2$	–	–

TABLE 2

^{1}H NMR and/or MS data of compounds of Table 1

Ex	^{1}H NMR (Solvent) ppm and/or MS
1	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.90 (d br, 1H); 8.01 (d, 1H); 7.75 (m, 2H); 7.59-7.24 (m, 11H); 5.35 (m, 1H); 3.54 (s, 2H); 2.50 (m, 4H); 2.07 (m, 5H); 1.55 (d, 3H) ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 451 (MH+); 226 (MHH++)
2	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.81 (d br, 1H); 8.00 (d, 1H); 7.74 (m, 2H); 7.56 (m, 3H); 7.49-7.36 (m, 5H); 6.93 (d, 2H); 5.30 (m, 1H); 3.78 (s, 3H); 3.48 (s, 2H); 2.41 (m, 4H); 1.98 (m, 4H); 1.53 (d, 3H) ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 481 (MH+)
3	^{1}H NMR (DMSO-d_6, 43 K; determined as trifluoroacetic salt) δ: 8.92 (d br, 1H); 8.42 (s br, 2H); 8.03 (d, 1H); 7.78 (m, 2H); 7.61-7.44 m, 6H); 7.31 (dd, 1H); 7.06 (m, 2H); 6.87 (dd, 1H); 5.32 (m, 1H); 3.79 (s, 3H); 3.63 (s br, 2H); 2.74 (m, 4H); 2.27 (m, 4H); 1.53 (d, 3H) ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 481 (MH+)
4	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.81 (d br, 1H); 8.00 (d, 1H); 7.74 (m, 2H); 7.56 (m, 3H); 7.49-7.36 (m, 3H); 7.15 (dd, 1H); 6.91 (d, 1H); 6.90 (s, 1H); 6.68 (d, 1H); 6.63 (s vbr, 1H); 5.26 (m, 1H); 3.52 (s, 2H); 2.44 (m, 4H); 2.01 (m, 4H); 1.52 (d, 3H) EI; TSQ 700; source 180°C;70 V;200 uA: 466 (M+.); 465; 424; 394; 380; 329; 300; 273; 261; 217.
5	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 457 (MH+)
6	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 467 (MH+)
7	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.67 (s br, 1H); 8.00 (d, 1H); 7.88 (d, 1H); 7.75 (dd, 1H); 7.62-7.54 (m, 5H); 7.51-7.35 (m, 5H); 7.27 (dd, 1H); 3.59 (s, 2H); 2.41 (m, 4H); 2.03 (m, 4H); 1.81 (s, 6H) ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 465 (MH+)
8	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 471 (MH+)
9	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 515 (MH+)
10	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 517 (MH+)
11	^{1}H NMR ($CDCl_3$) δ: 0.95 (d, 3H); 1.17 (d, 3H); 1.70-2.43 (m, 9H); 2.81 (t, 2H); 3.29 (t, 2H); 3.57 (s, 2H); 5.17 (m, 1H); 7.16-7.50

Ex	^{1}H NMR (Solvent) ppm and/or MS
	(m, 16H ar); 7.73 (td, 1H ar); 7.85-8.05 (m, 2H); 8.13 (dd, 1H ar)
12	^{1}H NMR ($CDCl_3$) δ: 1.48-2.25 (m, 8H); 1.72 (d, 3H); 2.85 (m, 4H); 3.23 (m, 4H); 3.66 (s, 2H); 5.53 (m, 1H); 6.22 (s, 1H); 7.28-7.65 (12H ar); 7.74 (t, 1H ar); 7.99 (d br, 1H); 8.12 (d, 1H ar)
13	^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 3H); 1.17 (d, 3H); 1.60-2.10 (m, 8H); 2.22 (m, 1H); 2.89 (m, 4H); 3.24 (m, 4H); 3.53 (m, 2H); 5.12 (m, 1H); 6.21 (s, 1H); 7.00-7.64 (12H); 7.72 (t, 1H ar); 7.90 (br, 1H ar); 8.12 (d, 1H ar)
14	^{1}H NMR ($CDCl_3$) δ: 1.10 (d, 3H); 1.72 (d, 3H); 1.88-2.49 (m, 11H); 2.70 (br, 1H); 3.64 (s, 2H); 5.53 (m, 1H); 7.25-7.52 (m, 8H ar); 7.53-7.81 (m, 3H); 8.01 (d, 1H ar); 8.14 (d, 1H ar)
15	^{1}H NMR ($CDCl_3$) δ: 1.23 (t, 3H); 1.45-2.25 (m, 8H); 1.72 (d, 3H); 2.41-3.32 (m, 8H); 3.47 (m, 1H); 3.66 (s, 2H); 4.11 (q, 2H); 5.53 (m, 1H); 6.10 (s, 1H); 7.25-7.55 (m, 11H); 7.59 (t, 1H ar); 7.77 (td, 1H ar); 7.99 (d, 1H ar); 8.13 (dd, 1H ar)
16	^{1}H NMR ($CDCl_3$) δ: 0.90 (d, 3H); 1.14 (d, 3H); 1.82-2.70 (m, 11H); 3.00 (td, 1H); 3.52 (s, 2H); 5.09 (t, 1H); 6.93 (br, 1H); 7.03-7.63 (m, 17H ar); 7.73 (t, 1H ar); 7.91 (br, 1H); 8.13 (d, 1H ar)
17	^{1}H NMR (DMSO-d_6) δ: 0.95-1.32 (m, 8H); 1.45 (m, 1H); 1.55-1.88 (m, 5H); 2.00-2.35 (m, 8H); 2.92 (m, 1H); 2.60-2.85 (m, 4H); 3.41 (br, 1H); 3.52 (s, 2H); 4.00 (m, 1H); 7.18 (m, 5H ar); 7.48-7.91 (m, 8H ar); 8.02 (d, 1H); 8.55 (d, 1H)
18	^{1}H NMR ($CDCl_3$) δ: 0.90-1.35 (m, 5H); 1.15 (d, 3H); 1.45 (m, 1H); 1.58-1.90 (m, 5H); 1.92-2.30 (m, 10H); 2.41 (t, 2H); 3.41 (br, 1H); 3.53 (s, 2H); 4.02 (m, 1H); 7.35-7.90 (m, 8H ar); 8.03 (d, 1H ar); 8.57 (d br, 1H)
19	^{1}H NMR ($CDCl_3$) δ: 1.00-2.00 (11H); 1.29 (d, 3H); 2.26 (m, 4H); 2.39 (m, 4H); 2.93 (s, 2H); 3.75 (s, 2H); 4.25 (m, 1H); 5.45 (br, 1H); 6.90 (br, 1H); 7.38-7.69 (m, 7H); 7.74 (t, 1H ar); 8.04 (d, 1H); 8.13 (d, 1H ar)
20	^{1}H NMR ($CDCl_3$) δ: 0.95-1.55 (m, 6H); 1.16 (t, 3H); 1.27 (d, 3H); 1.60-1.98 (5H); 2.02-2.55 (m, 8H); 3.09 (t, 1H); 3.67 (m, 1H); 3.73 (s, 2H); 4.00-4.36 (4H); 7.27 (m, 5H ar); 7.47 (m, 5H ar); 7.58 (t, 1H ar); 7.73 (t, 1H ar); 8.05-8.19 (m, 2H ar); 8.28 (br, 1H)
21	^{1}H NMR ($CDCl_3$) δ: 1.00-1.35 (m, 5H); 1.28 (d, 3H); 1.45 (m, 1H); 1.65-1.97 (m, 5H); 2.10-2.48 (m, 8H); 2.75 (t, 2H); 2.94 (s, 3H); 3.04 (t, 2H); 3.73 (s, 2H); 4.26 (m, 1H); 7.47 (m, 5H ar); 7.55 (br, 1H); 7.59 (t, 1H ar); 7.74 (t, 1H ar); 8.05 (d, 1H ar); 8.13 (d, 1H ar)
22	^{1}H NMR ($CDCl_3$) δ: 0.93-1.37 (m, 5H); 1.27 (d, 3H); 1.45 (m, 1H); 1.59-1.93 (m, 5H); 2.18-2.94 (9H); 2.98 (t, 1H); 3.66 (dd, 1H); 3.74 (s, 2H); 4.25 (m, 1H); 6.74 (br, 1H); 7.18-7.40 (m, 6H); 7.47 (m, 5H ar); 7.60 (td, 1H ar); 7.75 (td, 1H ar); 8.00 (dd, 1H ar); 8.15

Ex	^{1}H NMR (Solvent) ppm and/or MS
	(dd, 1H ar)
23	^{1}H NMR ($CDCl_3$) δ: 0.95-1.99 (m, 11H); 1.29 (d, 3H); 2.22-2.53 (m, 8H); 3.42 (s, 2H); 3.76 (dd, 2H); 4.28 (m, 1H); 7.48 (m, 5H ar); 7.59 (td and br, 2H); 7.76 (td, 1H ar); 8.08 (dd, 1H ar); 8.15 (dd, 1H)
24	^{1}H NMR (DMSO-d_6, 303K) δ: 8.55 (d br, 1H); 8.10 (dd, 1H); 7.70 (dt, 1H); 7.58-7.52 (m, 2H); 7.51-7.41 (m, 4H); 4.01 (m, 1H); 3.52 (s, 2H); 2.43 (m, 4H); 2.02 (m, 4H); 1.85-1.58 (m, 4H); 1.48 (m, 1H); 1.30-1.01 (m, 7H); 1.16 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 474 (M+); 432; 418; 390; 388; 347; 320; 291; 279; 235; 140; 85
25	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.33 (d br, 1H); 8.04 (d, 1H); 7.86 (d, 1H); 7.76 (dd, 1H); 7.57 (m, 2H); 7.51-7.41 (m, 3H); 4.05 (m, 1H); 3.56 (s, 2H); 2.45 (m, 4H); 2.04 (m, 4H); 1.87-1.61 (m, 5H); 1.54 (m, 1H); 1.34-1.06 (m, 6H); 1.20 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 490 (M+); 406; 336; 295; 280; 140; 85
26	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.53 (s br, 1H); 8.03 (d, 1H); 7.85 (d, 1H); 7.79 (dd, 1H); 7.66 (dd, 1H); 7.57-7.42 (m, 6H); 3.99 (m, 1H); 3.65 (s, 2H); 2.85 (m, 2H); 2.65 (s, 2H); 2.27 (m, 2H); 1.86-1.58 (m, 5H); 1.46 (m, 1H); 1.29-0.99 (m, 5H); 1.16 (d, 3H) ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 471 (MH+)
27	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 547 (MH+)
28	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.34 (d br, 1H); 8.03 (d, 1H); 7.87 (d, 1H); 7.79 (dd, 1H); 7.65 (dd, 1H); 7.46 (m, 5H); 3.99 (m, 1H); 3.78 (s, 2H); 3.15 (s, 4H); 2.88 (s, 3H); 1.84-1.59 (m, 5H); 1.47 (m, 1H);1.33-1.05 (m, 5H); 1.17 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 498 (M+); 372; 263; 246; 217
29	^{1}H NMR (DMSO-d_6, 343 K) δ: 10.61 (s br, 1H); 8.34 (d br, 1H); 8.04 (d, 1H); 7.87 (d, 1H); 7.79 (dd, 1H); 7.65 (dd, 1H); 7.50-7.43 (m, 5H); 4.00 (m, 1H); 3.78 (s, 2H); 3.01 (s, 4H); 1.85-1.59 (m, 5H); 1.49 (m, 1H); 1.32-1.03 (m, 5H); 1.18 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 484 (M+); 372; 357; 263; 246; 217
30	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.39 (d br, 1H); 8.03 (d, 1H); 7.85 (d, 1H); 7.79 (dd, 1H); 7.65 (dd, 1H); 7.50-7.39 (m, 5H); 4.73 (s br, 2H); 4.02 (m, 1H); 2.89 (s, 2H); 2.73 (m, 2H); 2.58 (t, 2H); 2.07 (s br, 1H); 1.85-1.59 (m, 5H); 1.50 (m, 1H); 1.32-1.03 (m, 5H); 1.20 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 470 (M+); 388; 370; 316; 287; 261
31	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.47 (d br, 1H); 8.04 (d, 1H); 7.86 (d, 1H); 7.81 (dd, 1H); 7.67 (dd, 1H); 7.59 (s br, 1H); 7.44 (m, 5H); 4.78-4.60 (m, 2H); 4.01 (m, 1H); 3.42 (s br, 2H); 3.38 (m, 2H); 1.84-1.60 (m, 5H); 1.51 (m, 1H); 1.34-1.03 (m, 5H); 1.20 (d,

Ex	^{1}H NMR (Solvent) ppm and/or MS
	3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 484 (M+); 401; 370; 330; 300; 273; 217
32	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.32 (d br, 1H); 8.10 (dd, 1H); 7.67 (dt, 1H); 7.55-7.43 (m, 6H); 7.22 (s br, 1H); 4.02 (m, 1H); 3.70 (s, 2H); 2.90 (m, 2H); 2.69 (s, 2H); 2.31 (m, 2H); 1.86-1.61 (m, 5H); 1.51 (m, 1H); 1.32-1.05 (m, 5H); 1.19 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 488 (M+); 390; 262; 279; 264; 235
33	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.53 (s br, 1H); 8.03 (d, 1H); 7.83 (d, 1H); 7.79 (dd, 1H); 7.66 (d, 1H); 7.50 (m, 2H); 7.49 (m, 3H); 7.34 (dd, 2H); 7.26 (dd, 1H); 7.11 (d, 2H); 4.40 (s, 2H); 3.99 (m, 1H); 3.67 (s, 2H); 2.89 (m, 2H); 2.82 (s, 2H); 2.36 (m, 2H); 1.83-1.58 (m, 5H); 1.44 (m,1H); 1.28-0.99 (m, 8H) EI; TSQ 700; source 180 C;70 V;200 uA: 560 (M+·); 469; 372; 263; 217
34	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.54 (s br, 1H); 8.09 (d, 1H); 7.85 (d, 1H); 7.71 (dd, 1H); 7.56-7.43 (m, 6H); 3.98 (m, 1H); 3.64 (s, 2H); 2.85 (m, 2H); 2.65 (s, 2H); 2.26 (m, 2H); 1.83-1.58 (m, 5H); 1.45 (m, 1H); 1.28-0.98 (m, 5H); 1.15 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 504 (M+); 406; 297; 280; 253
35	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.55 (s br, 1H); 7.89 (dd, 1H); 7.78 (dd, 1H); 7.62 (dt, 1H); 7.55-7.44 (m, 6H); 3.99 (m, 1H); 3.64 (s, 2H); 2.85 (m, 2H); 2.65 (s, 2H); 2.26 (m, 2H); 1.83-1.58 (m, 5H); 1.44 (m, 1H); 1.28-0.98 (m, 5H); 1.15 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 488 (M+); 390; 334; 281; 264; 235
36	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.36 (d br, 1H); 8.02 (d, 1H); 7.86 (d, 1H); 7.78 (dd, 1H); 7.64 (dd, 1H); 7.55-7.43 (m, 5H); 4.02 (m, 1H); 3.67 (s, 2H); 3.14 (dd, 2H); 2.97 (m, 2H); 2.74 (s, 2H); 2.38 (m, 2H); 1.86-1.60 (m, 5H); 1.49 (m, 1H); 1.41 (m, 2H); 1.29-1.26 (m, 5H); 1.18 (d, 3H); 0.78 (t, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 512 (M+); 372; 263; 246; 217; 141
37	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.52 (d br, 1H); 8.03 (d, 1H); 7.85 (d, 1H); 7.79 (dd, 1H); 7.66 (dd, 1H); 7.54-7.42 (m, 5H); 4.58 (t, 1H); 3.99 (m, 1H); 3.63 (s, 2H); 3.39 (m, 2H); 3.21 (m, 2H); 3.06 (m, 2H); 2.72 (s, 2H); 2.35 (m, 2H); 1.84-1.58 (m, 5H); 1.45 (m, 1H); 1.28-0.99 (m, 8H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 514 (M+); 372; 261; 246; 217
38	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.46 (d br, 1H); 7.52-7.40 (m, 6H); 7.39 (s, 1H); 7.17 (s, 1H); 4.39 (s, 4H); 3.96 (m, 1H); 3.58 (s, 2H); 2.86 (m, 2H); 2.64 (s, 2H); 2.24 (m, 2H); 1.83-1.57 (m, 5H); 1.45 (m, 1H); 1.30-0.99 (m, 5H); 1.13 (d, 3H)

Ex	^{1}H NMR (Solvent) ppm and/or MS
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 528 (M+); 430; 345; 319; 304; 277
39	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.31 (d br, 1H); 7.70-7.45 (m, 8H); 7.21 (s br, 1H); 4.02 (m, 1H); 3.70 (s, 2H); 2.89 (m, 2H); 2.69 (s, 2H); 2.31 (m, 2H); 1.86-1.61 (m, 5H); 1.50 (m, 1H); 1.33-1.07 (m, 5H); 1.19 (d, 3H)
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 488 (M+); 390; 291; 281; 264; 235
40	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.92 (d br, 1H); 8.02 (d, 1H); 7.75 (dd, 1H); 7.71 (d br, 1H); 7.59-7.41 (m, 8H); 7.38 (dd, 2H); 7.28 (dd, 1H); 7.15 (s br, 1H); 5.08 (dt, 1H); 3.58 (s, 2H); 2.81 (m, 2H); 2.54 (s, 2H); 2.17 (m, 2H); 1.88 (m, 2H); 0.96 (t, 3H)
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 478 (M+); 433; 380; 351; 261; 246; 217
41	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.59 (d br, 1H); 8.01 (d, 1H); 7.92 (m, 1H); 7.82-7.61 (m, 5H); 7.21 (dd, 1H); 4.08-3.70 (m, 3H); 3.11-2.76 (m, 4H); 2.53 (s, 2H); 1.83-1.59 (m, 5H); 1.47 (m, 1H); 1.28-1.01 (m, 5H); 1.17 (d, 3H)
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 476 (M+); 378; 322; 288; 252
42	^{1}H NMR (DMSO, 343 K) δ : 8.94(d br, 1H); 8.01(d, 1H); 7.75(dd, 1H); 7.64 (m, 1H); 7.57-7.25 (m, 11H); 7.12 (s br, 1H); 4.90 (t, 1H); 3.51 (s br, 2H); 2.77 (m, 2H); 2.50 (s, 2H); 2.10 (m, 3H); 1.09 (d, 3H); 0.84 (d, 3H)
	EI; TSQ 700; source 180 C;70 V;200 uA: 492 (M+.); 351; 261; 246; 217; 133
43	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.29 (d br, 1H); 8.02 (d, 1H); 7.88 (d, 1H); 7.77 (dd, 1H); 7.64 (dd, 1H); 7.54 (m, 2H); 7.46 (m, 3H); 4.03 (m, 1H); 3.66 (s, 2H); 3.27 (t, 2H); 3.06 (m, 2H); 2.74 (s, 2H); 2.38 (m. 2H); 2.32 (m, 6H); 1.87-1.60 (m, 5H); 1.54-1.33(m, 7H); 1.29-1.04(m, 5H); 1.19(d, 3H).
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 581 (M+); 427; 210; 111; 98
44	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.31 (d br, 1H); 8.03 (d, 1H); 7.87 (d, 1H); 7.78 (dd, 1H); 7.64 (dd, 1H); 7.61 (dd, 2H); 7.27 (dd, 2H); 7.26 (s br, 1H); 4.03 (m, 1H); 3.68 (s, 2H); 2.91 (m, 2H); 2.71 (s, 2H); 2.34 (m, 2H); 1.86-1.61 (m, 5H); 1.51 (m, 1H); 1.32-1.05 (m, 5H); 1.20 (d, 3H)
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 488 (M+.); 390; 281; 264; 235
45	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.33 (d br, 1H); 8.05 (d, 1H); 7.89 (d, 1H); 7.79 (m, 5H); 7.67 (dd, 1H); 7.21 (s br, 1H); 4.05 (m, 1H); 3.70 (s, 2H); 2.85 (m, 2H); 2.68 (s, 2H); 2.32 (m, 2H); 1.88-1.61 (m, 5H); 1.51 (m, 1H); 1.34-1.05 (m, 5H); 1.21 (d, 3H)
	EI; TSQ 700; source 180 C; 70 V; 200 uA: 538 (M+); 440; 412; 366; 331; 314; 285
46	^{1}H NMR (DMSO-d_6, 343 K) δ: 8.39 (d br, 1H); 8.04 (d, 1H); 7.88 (d, 1H); 7.79 (dd, 1H); 7.67 (dd, 1H); 7.54-7.40 (m, 2H); 7.34-

Ex	^{1}H NMR (Solvent) ppm and/or MS
	7.21 (m, 2H); 7.20 (s br, 1H); 4.04 (m, 1H); 3.58 (s, 2H); 2.88 (m, 2H); 2.64 (s, 2H); 2.29 (m, 2H); 1.89-1.60 (m, 5H); 1.51 (m, 1H); 1.38-1.06 (m, 5H); 1.20 (d, 3H) EI; TSQ 700; source 180 C; 70 V; 200 uA: 488 (M+); 384

TABLE 3

Chemical names of parent compounds of Table 1 (names generated by Beilstein's Autonom)

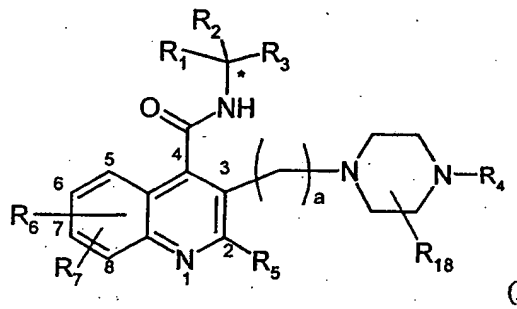
Ex	Chemical name
1	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide
2	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(4-methoxy-phenyl)-ethyl]-amide
3	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-amide
4	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(3-hydroxy-phenyl)-ethyl]-amide
5	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((R)-1-cyclohexyl-ethyl)-amide
6	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid [(S)-1-(4-hydroxy-phenyl)-ethyl]-amide
7	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid (1-methyl-1-phenyl-ethyl)-amide
8	2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid (1-cyclohexyl-1-methyl-ethyl)-amide
9	7-Phenyl-8-piperazin-1-ylmethyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
10	6,7-Dimethoxy-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
11	2-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-ethanesulfonic acid phenyl ester
12	3-[4-(2-Nitro-1-pyrrolidin-1-yl-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide
13	3-[4-(2-Nitro-1-pyrrolidin-1-yl-vinyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide
14	2-Methyl-3-{4-[2-phenyl-4-((S)-1-phenyl-ethylcarbamoyl)-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid
15	1-(2-Nitro-1-{4-[2-phenyl-4-((S)-1-phenyl-ethylcarbamoyl)-quinolin-3-ylmethyl]-piperazin-1-yl}-vinyl)-piperidine-3-carboxylic acid ethyl ester
16	3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid
17	2-Benzyl-3-{4-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid
18	3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-propionic acid
19	3-(4-Carbamoylmethyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

Ex	Chemical name
20	3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid ethyl ester
21	3-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
22	3-{4-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-yl}-2-phenyl-propionic acid
23	3-(4-Cyanomethyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
24	6-Fluoro-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
25	6-Chloro-2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
26	3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
27	3-(3-Oxo-4-phenyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
28	3-(4-Methyl-3,5-dioxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
29	3-(3,5-Dioxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
30	3-(2-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
31	3-(2,5-Dioxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
32	6-Fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
33	3-(4-Benzyl-3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
34	7-Chloro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
35	7-Fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
36	3-(3-Oxo-4-propyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
37	3-[4-(2-Hydroxy-ethyl)-3-oxo-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide dihydrochloride
38	8-(3-Oxo-piperazin-1-ylmethyl)-7-phenyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
39	8-Fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
40	3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide
41	3-(3-Oxo-piperazin-1-ylmethyl)-2-thiophen-2-yl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

Ex	Chemical name
42	3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide
43	3-[3-Oxo-4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid ((S)-cyclohexyl-ethyl)-amide
44	2-(4-Fluoro-phenyl)-3-(3-oxo-piperazin-1-ylmethyl)-quinoline-4-carboxylic acid ((S)-cyclohexyl-ethyl)-amide
45	3-(3-Oxo-piperazin-1-ylmethyl)-2-(4-trifluoromethyl-phenyl)-quinoline-4-carboxylic acid ((S)-cyclohexyl-ethyl)-amide
46	2-(2-Fluoro-phenyl)-3-(3-oxo-piperazin-1-ylmethyl)-quinoline-4-carboxylic acid ((S)-cyclohexyl-ethyl)-amide
47	3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-6--trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
48	3-(3-Oxo-piperazin-1-ylmethyl)-2-phenyl-7-trifluoromethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide

CLAIMS

1. A compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

wherein:

R_1 is H or alkyl;

R_2 is aryl or cycloalkyl or heteroaryl, optionally substituted one or more times by alkyl, OH or alkoxy;

R_3 is H or alkyl or cycloalkyl or cycloalkylalkyl, optionally substituted one or more times by hydroxy or by one or more fluorines;

R_4 is H, or $-R_8R_9$ where R_8 is optionally substituted one or more times by R_{13}, or R_{19};

R_8 is alkyl or alkenyl;

R_9 is $S(O_2)R_{10}$, $S(O_2)OR_{10}$, ONO, $C(O)OR_{10}$, $C(O)NR_{11}R_{12}$, or CN;

R_{10} is H, alkyl, aryl or cycloalkyl;

R_{11} and R_{12} are independently selected from H and alkyl;

R_{13} is R_{14} or $-R_{14}R_{15}$;

R_{14} is alkyl, aryl, cycloalkyl, arylalkyl, or a five-, six-, seven- or eight-membered heterocyclic ring comprising one or more heteroatoms selected from N, O and S;

R_{15} is alkyl or $-R_{16}COOR_{17}$;

R_{16} is a single bond or alkyl;

R_{17} is H or alkyl;

R_{18} is H or up to three oxo substituents;

R_{19} is R_{20} or $-R_{20}R_{21}$;

R_{20} is alkyl, alkenyl or a single bond;

R_{21} is OH, aryl, cycloalkyl or a saturated heterocyclic ring comprising one or more heteroatoms selected from N, O and S;

R_5 is a alkyl, cycloalkyl, cycloalkylalkyl, aryl, or single or fused ring aromatic heterocyclic group, which group may be substituted one or more times by halo, hydroxy, alkyl or alkyl substituted one or more times by halo or hydroxy;

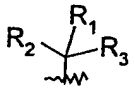
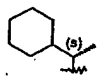
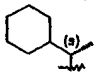
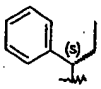
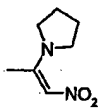
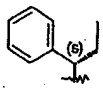
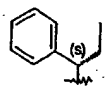
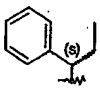
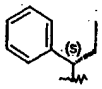
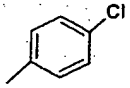
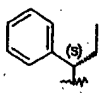
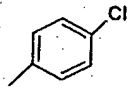
R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy or a hydroxylated derivative thereof, hydroxy, halogen, nitro, cyano, carboxy, alkylcarboxy, alkylcarboxyalkyl, haloalkyl such as trifluoromethyl, amino or mono- or di- alkylamino; or R_6 represents a bridging moiety which is arranged to bridge two adjacent ring atoms, which bridging moiety comprises alkyl or dioxyalkylene;

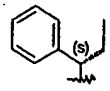
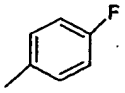
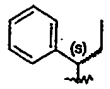
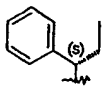
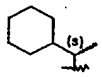
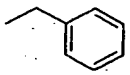
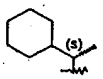
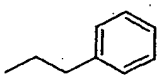
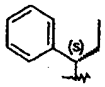
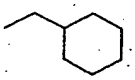
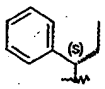
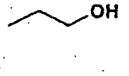
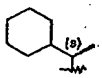
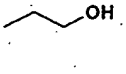
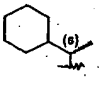
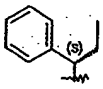
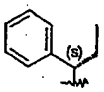
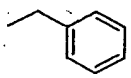
R_7 is H or halo;

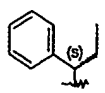
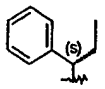
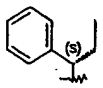
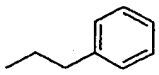
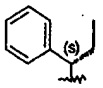
a is 1-6; and

any of R_2, R_5, R_8, R_{10}, R_{11}, R_{12}, R_{14}, R_{16}, R_{17} and R_{21} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

subject to the proviso that said compound is not a compound wherein R_7 represents H, R_5 represents unsubstituted phenyl, R_{18} is H, and R_1, R_2, R_3 and R_4 are one of the following combinations:

	a	R_4	R_6
	1		H
	1	H	H
	1	H	H
	1		H
	2		H
	3		H
	4		H
	3		H
	2		H

	2		H
	3		OMe
	1		H
	1		H
	1		H
	1		H
	1		H
	1		H
	1	Et	H
	1	Me	H
	1		H

	2	Me	H
	1	Et	H
	1		H
	3		OH

2. A compound as claimed in claim 1, wherein R_3 represents methyl, ethyl, isopropyl, cyclopropyl, hydroxymethyl or hydroxyethyl.

3. A compound as claimed in claim 1 or claim 2, wherein R_2 represents phenyl or cyclohexyl.

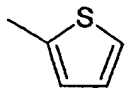
4. A compound as claimed in claim 3, wherein R_2 represents phenyl which is meta- or para-substituted once by –OMe or –OH.

5. A compound as claimed in any preceding claim, wherein R_1 is hydrogen or methyl.

6. A compound as claimed in any preceding claim, wherein R_5 is phenyl which is unsubstituted or which is substituted one or more times by halo such as fluoro and/or by haloalkyl such as trifluoromethyl.

7. A compound as claimed in any of claims 1-5, wherein R_5 is a heterocyclic ring, such as an unsaturated heterocyclic ring, comprising at least one heteroatom such as S.

8. A compound as claimed in claim 7, wherein R_5 is



9. A compound as claimed in any preceding claim, wherein R_7 represents hydrogen.

10. A compound as claimed in any preceding claim, wherein R_6 represents hydrogen or one or more substituents selected from fluoro, chloro, bromo or trifluoromethyl.

11. A compound as claimed in claim 10, wherein each of said one or more substituents is respectively positioned at the 5', 6', 7' or 8' position around the quinoline ring of said compound.

12 A compound as claimed in any of claims 1-9, wherein R_6 represents one ring substituent, which is hydroxy, alkoxy such as methoxy or ethoxy or a hydroxylated derivative thereof, alkoxycarboxylate such as methoxycarboxylate or ethoxycarboxylate or an esterified derivative thereof such as methoxyethanoate ethoxyethanoate, or alkoxyamido such as methoxyamido or ethoxyamido.

13. A compound as claimed in claim 12, wherein said one ring substituent is located at the 6 or 7 position around the quinoline ring of said compound.

14. A compound as claimed in any preceding claim, wherein a is 1, 2 or 3.

15. A compound as claimed in any preceding claim, wherein R_4 is hydrogen.

16. A compound as claimed in any preceding claim, wherein R_8 is methyl, ethyl, ethenyl or propenyl.

17. A compound as claimed in any preceding claim, wherein R_9 is C(O)OH or $C(O)NH_2$.

18. A compound as claimed in any of claims 1-16, wherein R_9 is $S(O_2)R_{10}$, $S(O_2)OR_{10}$, or $C(O)OR_{10}$, and R_{10} is phenyl, methyl or ethyl.

19. A compound as claimed in any of claims 1-16, wherein R_9 is $C(O)NR_{11}R_{12}$ and each of R_{10} and R_{11} is the same one of methyl or ethyl.

20. A compound as claimed in any of claims 1-19, wherein R_4 is branched or linear $R_8(R_{13})R_9$, R_{13} is R_{14} and R_{14} is C_{1-6} alkyl, or phenyl, or phenylmethyl, or phenylethyl.

21. A compound as claimed in claims 1-19, wherein R_4 is branched or linear $R_8(R_{13})R_9$, R_{13} is $R_{14}R_{15}$, and R_{14} is a five- or six-membered saturated heterocyclic ring.

22. A compound as claimed in claim 21, wherein said heterocyclic ring comprises one or more N atoms.

23. A compound as claimed in claim 21, wherein said heterocyclic ring is N-linked to said R_8.

24. A compound as claimed in any of claims 1-19, wherein R_4 is branched or linear $R_8(R_{13})R_9$, R_{13} is $-R_{14}R_{15}$, and R_{14} is C_{1-6} alkyl, or phenyl, or phenylmethyl, or phenylethyl.

25. A compound as claimed in any of claims 21-24, wherein R_{15} is hydrogen, methylethanoate, ethylethanoate, propylethanoate or butylethanoate.

26. A compound as claimed in any preceding claim, wherein R_{20} is a single bond and R_{21} is aryl such as phenyl.

27. A compound as claimed in any of claims 1-25, wherein R_{20} is straight chain alkyl such as methyl, ethyl or propyl, and R_{21} is OH, aryl, or a saturated heterocyclic ring comprising one or more N heteroatoms.

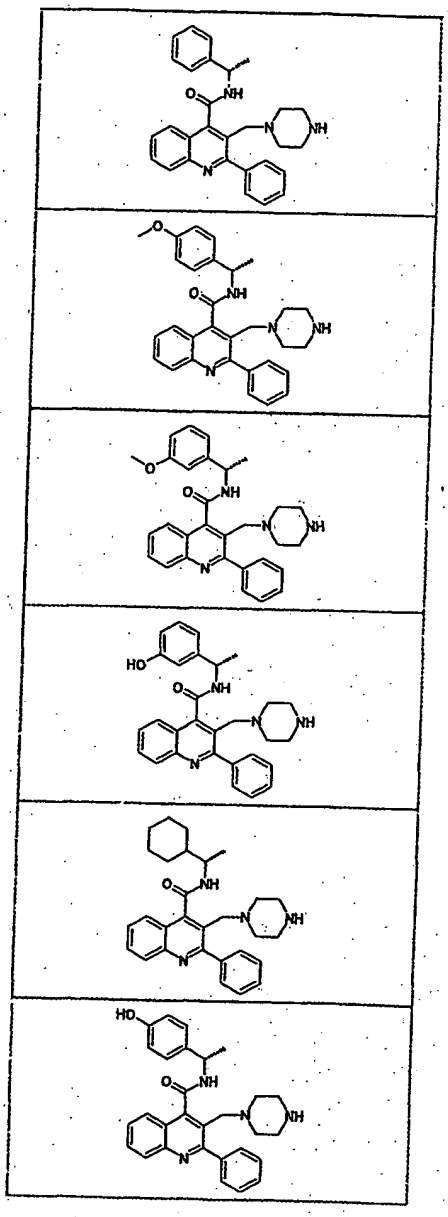
28. A compound as claimed in any preceding claim, wherein R_{18} is H.

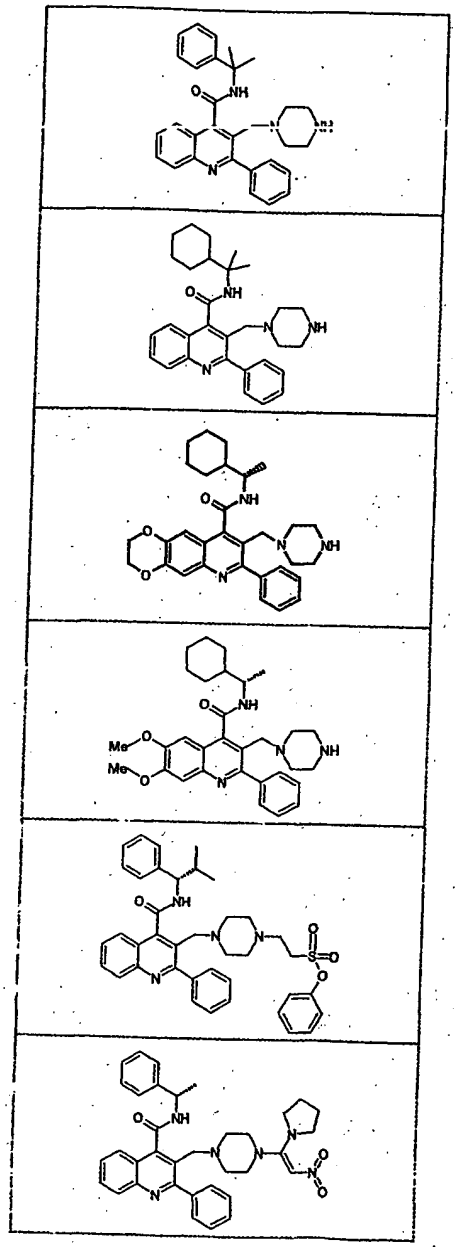
29. A compound as claimed in any of claims 1-27, wherein R_{18} represents one or more oxo substituents.

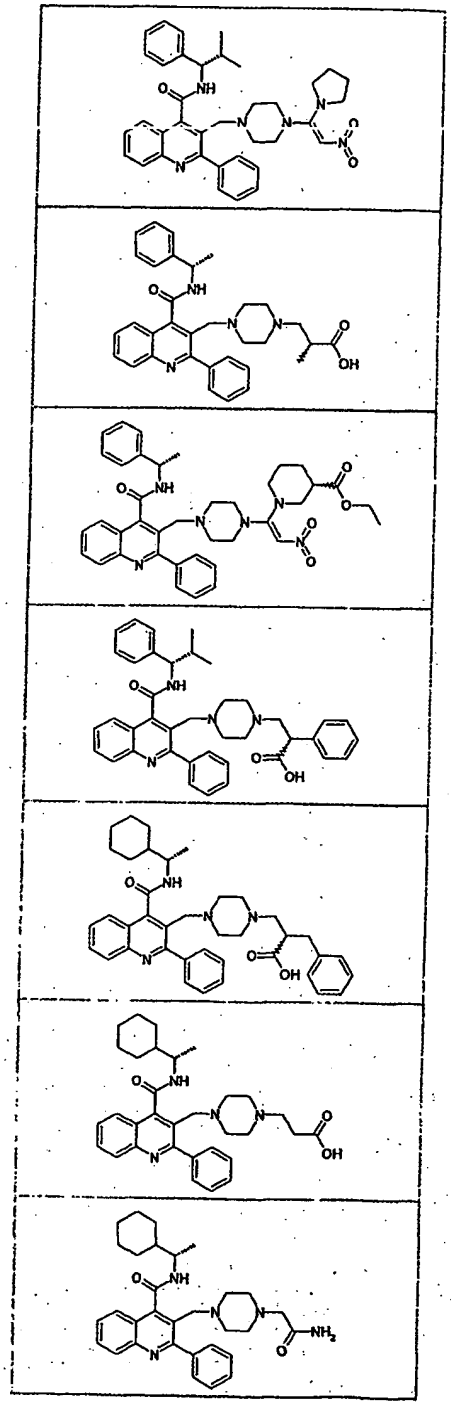
30. A compound as claimed in claim 29, wherein R_{18} represents one oxo substituent which is positioned at the 3', 5' or 6' position around the piperazine ring of said compound.

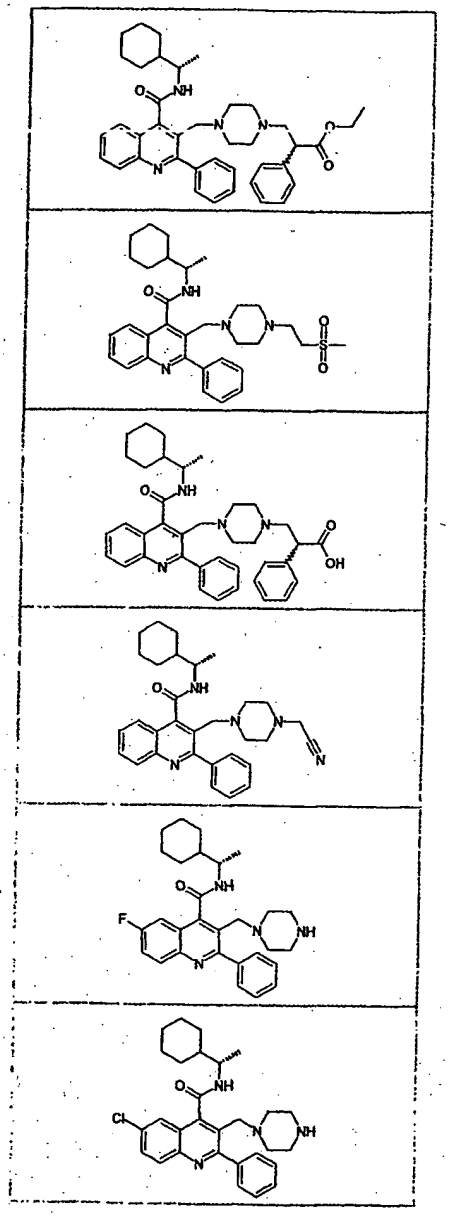
31. A compound as claimed in claim 29, wherein R_{18} represents two oxo substituents which are respectively positioned at the 3' and 5' or at the 3' and 6' positions around the piperazine ring of said compound.

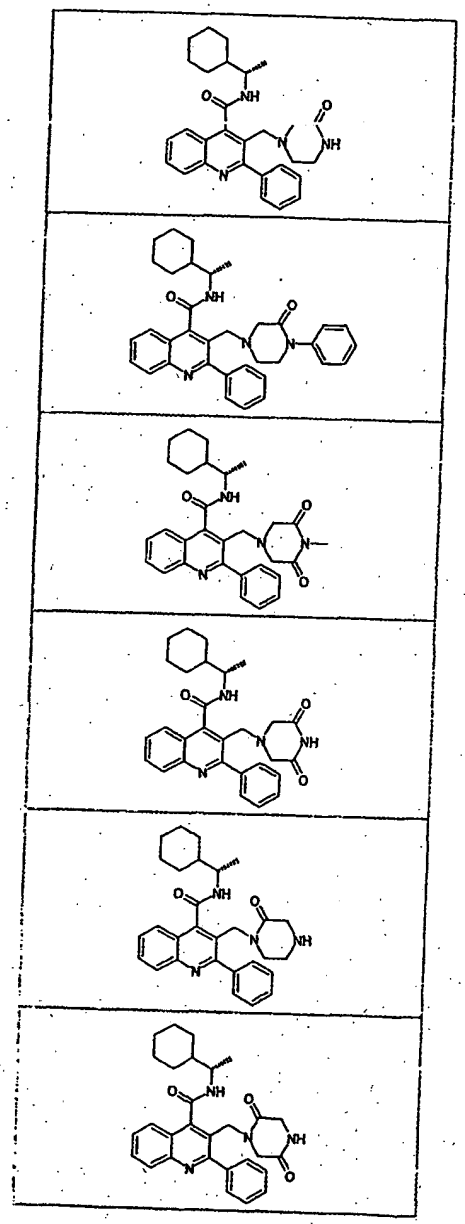
32. A compound as claimed in any preceding claim, which is selected from the following:

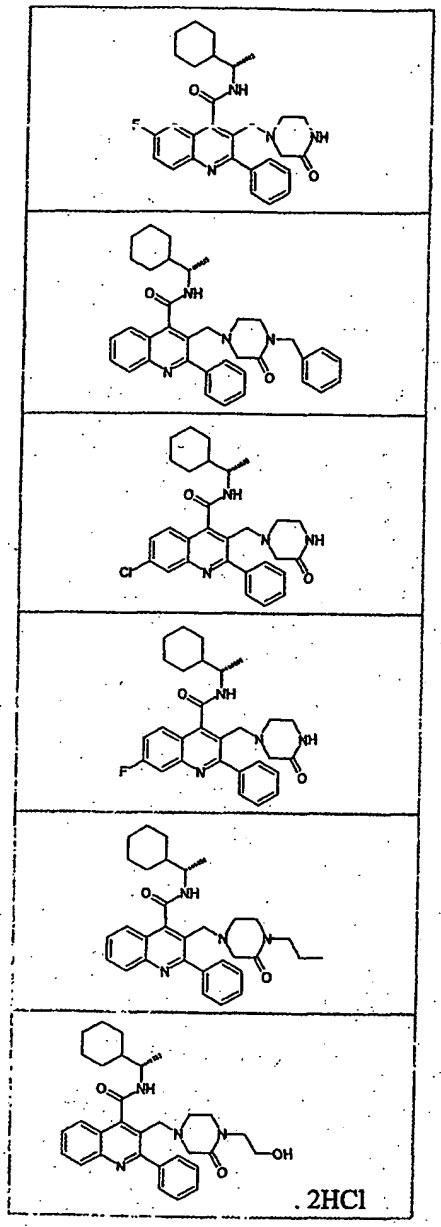


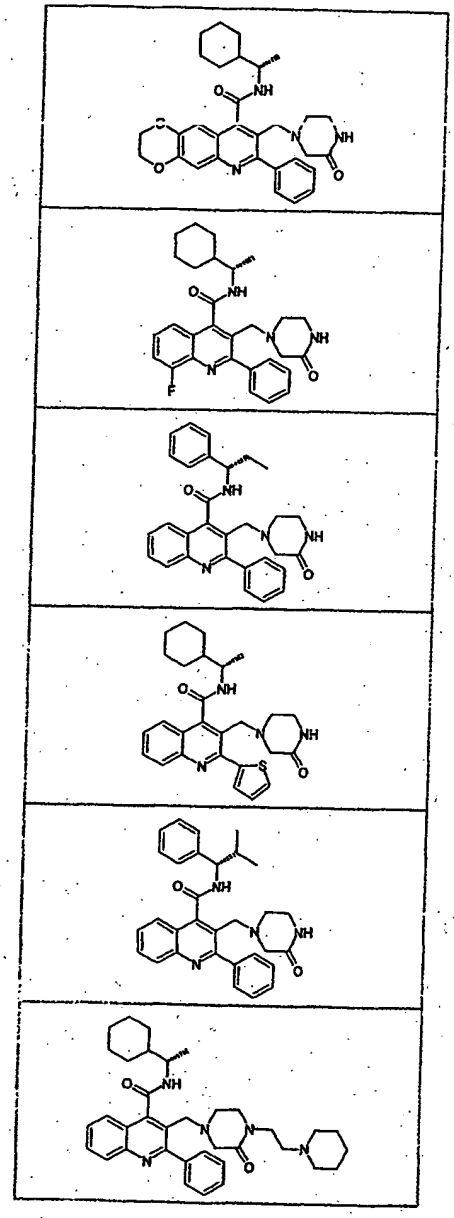


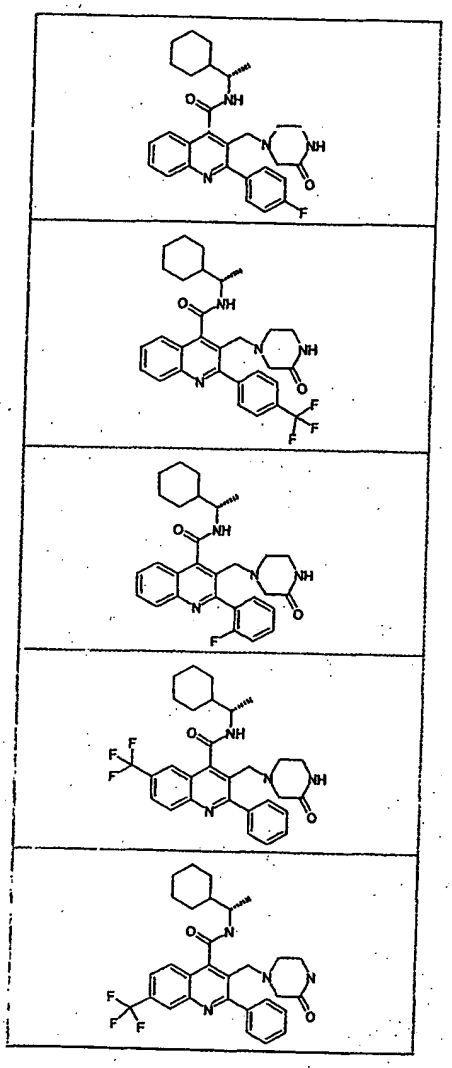




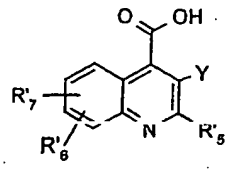



. 2HCl



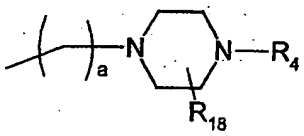


33. A process for the preparation of a compound of formula (I) according to any of claims 1-32, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



(II)

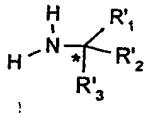
wherein R'5, R'6, and R'7 are R5, R6, and R7 respectively as defined in relation to formula (I) or a group convertible to R5, R6, and R7 respectively, and Y' is a group of formula (Y) or a group convertible thereto



(Y)

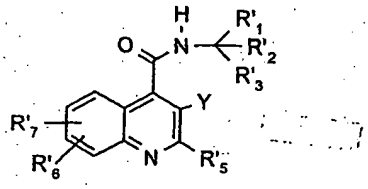
wherein R4 and R18 are defined as in relation to formula (I) above,

with a compound of formula (III):



(III)

wherein R'1, R'2 and R'3 are R1, R2 and R3 as defined for formula (I) or a group or atom convertible to R1, R2 and R3 respectively; to form a compound of formula (Ib):



(Ib)

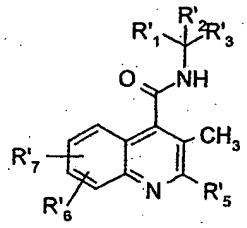
wherein R'_1, R'_2, R'_3, R'_5, R'_6, R'_7 and Y' are as defined above, and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, R'_5, R'_6, R'_7 and Y' to R_1, R_2, R_3, R_5, R_6, R_7 and Y respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

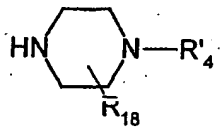
(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

34 A process for the preparation of a compound of formula (I) according to any of claims 1-32, wherein a is 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (T) or an active derivative thereof:



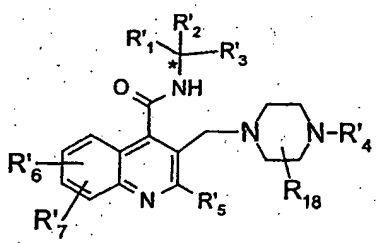
(T)

wherein each of R'_1, R'_2, R'_3, R'_5, R'_6, and R'_7 is R_1, R_2, R_3, R_5, R_6, or R_7 respectively as defined in relation to formula (I) or a group convertible to R_1, R_2, R_3, R_5, R_6, or R_7 respectively, providing that R_2 is not an aromatic group, with a compound of formula (W)



(W)

wherein R'4 is a group R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, and R_{18} is a group R_{18} as defined in relation to formula (I), to form a compound of formula (Ib):



(Ib)

and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'1, R'2, R'3, , R'4, R'5, R'6, and R'7 to R_1, R_2, R_3, R_4, R_5, R_6, and R_7 respectively as required, to obtain a compound of formula (I) as claimed in claim 1;

(ii) converting a compound of formula (I) as claimed in claim 1 into another compound of formula (I) as claimed in claim 1; and

(iii) preparing a salt of the compound of formula (I) as claimed in claim 1 and/or a solvate thereof.

35. A pharmaceutical composition comprising a compound of formula (I) according to any of claims 1-32, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

36. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

37. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

38. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

39. A method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 01/13833

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/06 A61K31/495 A61P25/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 52942 A (RAVEGLIA LUCA FRANCESCO ;GRAZIANI DAVIDE (IT); GRUGNI MARIO (IT);) 26 November 1998 (1998-11-26) ex. 11-14,20,22-24,26-30,35-37,39-40, 42-43 page 1, line 19 - line 24	1-39
X	WO 00 31037 A (NADLER GUY MARGUERITE MARIE G ;MORVAN MARCEL (FR); SMITHKLINE BEEC) 2 June 2000 (2000-06-02) cited in the application cf. ex. 1,3-10,16-17,28-29,37,65 cf. especially ex. 34,92 page 1, paragraph 5	1-39

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2002	12/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 01/13833

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